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STUDIES IN DIABETES MELLITUS.

II. Its Incidence and the Factors Underlying Its Variations.

By Elliott P. Joslin, M.D.,

CLINICAL PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; MEDICAL DIRECTOR OF THE GEORGE F. BAKER CLINIC, NEW ENGLAND DEACONESS HOSPITAL, BOSTON, MASS.

Louis I. Dublin, Ph.D.,

THIRD VICE PRESIDENT AND STATISTICIAN, METROPOLITAN LIFE INSURANCE COMPANY,

AND

Herbert H. Marks,

NEW YORK.

(From The George F. Baker Clinic, New England Deaconess Hospital and the Statistical Bureau, Metropolitan Life Insurance Company.)

Our earlier paper dealt with the characteristics and trends of diabetes mortality. Of equal interest and value are the facts on the morbidity or incidence of the disease in various parts of the world, and in various geographical, social and economic groups. These we shall now consider. We may, then, be in a position to discuss the underlying reasons for these differences.

Incidence of Diabetes in the United States. To assess the size of the diabetes problem, it is necessary to know the number of persons who suffer from it. This would be a simple matter if its reporting were compulsory as is the case with certain of the communicable diseases. But since this is not done and is indeed not practicable, we are compelled to resort to other methods. Various estimates

of the number of diabetics have been made for many countries and they differ widely. In the United States, the highest estimate (1% of the population) is unquestionably excessive. It will be worthwhile to examine the available facts which throw light on this important question to see if some reasonable estimate can be made.

First, an approximation of the number of cases may be made from the number of deaths and the average duration of the disease. At the present time, the annual recorded death toll from diabetes in the United States is about 27,000. The true number is considerably higher. Some deaths from diabetes are missed because of faulty diagnosis. In other cases, where the diabetes is under control, the physician may report that the patient died of heart disease, chronic nephritis, cancer or some other diseases of later life, which often complicate diabetes and the death is charged to one of these other causes. The actual number of deaths of diabetics annually may, therefore, run as high as 30,000. The second item of the computation, the duration of the disease, is also uncertain. In Joslin's experience the average duration in fatal cases in the period 1922 to 1926 was 7.6 years, but from 1926 to 1930, 8.4 years. The average duration of these fatal cases is still on the increase and the true figure is now higher than Joslin's latest average. Certainly there has been going on a marked improvement in the duration of life among all classes of diabetics, especially children, since the use of insulin has become general. The average duration of fatal cases today, therefore, is probably more than the previous expectation of life of diabetics. In view of all of the circumstances, we believe that an average of 10 years' duration between onset and death is a conservative estimate. The number of cases today on this basis would approximate the number of deaths per year times the average duration, or 27,000 to 30,000 $\times$ 10, or between 270,000 and 300,000 cases.

The several sickness surveys, made from time to time, in various areas are also of value in estimating the incidence of diabetes. The survey of chronic disease in Massachusetts in recent years under the direction of Bigelow and Lombard[1] of the State Department of Health gives us the fullest information on this subject. For this survey, house to house visits were made in various areas of the State and a mixed rural and urban population of approximately 100,000 persons was covered. Special attention was paid to persons over 40 because the investigators were primarily interested in chronic disease. On the basis of this investigation, it was estimated that there were 15,000 diabetics in Massachusetts, or nearly 4 cases of the disease per 1000 inhabitants.

Details regarding age and sex incidence of the Massachusetts survey were available to us through the courtesy of Dr. Lombard. At ages 40 and over, there were twice as many female diabetics as there were males. In both sexes, more than half the cases were

between 50 and 69 years of age, but the age incidence of the disease, relative to the number of persons living, was highest between ages 70 and 79. In that age period, the ratio of diabetic to the total population surveyed was 10.4 for males and 19 per 1,000* for females. These ratios show a steady rise with age. Between 40 and 49 only 4.2 men and 5 women per M were diabetic. Under age 40 the number of diabetics counted in this survey was too small to be representative; at ages under 20, there were only 6 cases (0.4 per M), and between ages 20 and 39, 20 cases (1.5 per M).

The number of diabetics in the United States would be 500,000, if the incidence of 4 per M registered in Massachusetts prevailed throughout the country. But the population of Massachusetts is older on the average than is the country as a whole. Fortunately, we can bring our estimate a little closer by using the incidence rates, specific for sex and age. This gives between 350,000 and 400,000 diabetics as the probable number. This figure is derived in the following manner: For ages over 40, the incidence in Massachusetts at the various ages for each sex separately has been multiplied by the corresponding populations for the country. Thus, we obtain a total of approximately 325,000 diabetics at ages 40 and over, of whom $\frac{2}{5}$ are men and $\frac{3}{5}$, women (see Table 1). For ages under 40, there would be about 75,000 cases on the basis of the Massachusetts figures, but the basis of the computation cannot be considered very reliable. Some clue to the number of cases at these ages is furnished, however, by the mortality figures in the years preceding insulin treatment. At that time, few young diabetics survived more than a year, particularly at ages under 20. The number of new cases each year is, therefore, approximately equal to the annual toll of deaths from diabetes at that time. Between 1919 and 1921 the average number was 1,400 at ages under 20 and nearly 2,000 between ages 20 and 39. Making allowance for the mortality under present conditions of young diabetics acquiring the disease since 1921, and for the fact that with the lapse of time some of those surviving have graduated into the succeeding age groups, the number of diabetics under 20 may be taken as between 4 and 6 times the annual pre-insulin toll of 1,400, at these ages or between 5,600 and 8,400; and at ages 20 to 39, between 8 and 10 times the 2,000 deaths occurring annually prior to 1922, or between 16,000 and 20,000. The total under 40 by this estimate would be roughly between 22,000 and 30,000.

While the Massachusetts survey is the most comprehensive and most detailed, it will be worthwhile to review other surveys which throw light on this problem of diabetes incidence. Two such studies[2,3] in New York State in 1927 are informative. In Essex County, which is largely rural in nature, investigation disclosed 154

* Throughout this and other papers of the series "per M" is used to indicate "per thousand persons."

cases of diabetes in a population of approximately 18,000, or nearly 9 cases per M. This county, however, contains an exceptionally large proportion of old persons and we know that the existence of the disease rises rapidly with age. The incidence figure for this county, therefore, is probably higher than average. The second survey in New York State covering a larger area also rural in character, revealed a total of 505 diabetics in an estimated population of 101,000, or an incidence of 5 diabetics per M. This population, too, contained an unduly large proportion of older persons and is also probably higher than the average for the country. The survey of chronic illness in New York City[4] in 1928 covering 20,754 persons chronically ill disclosed 378 (18.2 per M) with diabetes. Of this number, 326 were suffering primarily from diabetes, but in 52 others the diabetes complicated some more serious condition. This high proportion is, one must remember, the incidence of diabetes among persons incapacitated by illness, and not in a general population. Surveys of small populations in Massachusetts[5,6] in 1927 disclosed between 1 and 2 diabetics per M. In the well-known Hagerstown sickness study[7] covering 8,600 persons, 16 cases of diabetes were found (nearly 2 per M).

TABLE 1.—ESTIMATED INCIDENCE OF DIABETES IN THE UNITED STATES, 1930. AGES 40 AND OVER. BY SEX.

	Massachusetts survey.			United States.	
		Incidence of diabetes.			
Sex, age group.	Population covered.	Number of cases.	Cases per 1,000 population.	Population 1930 Census.	Estimated number of diabetics on basis of Massachusetts incidence.
Persons					
Ages 40 and over	45,487	445	....	36,038,981	325,711
Males:					
40 and over	21,220	146	....	18,632,739	123,765
40 to 49	8,048	34	4.2	7,808,383	32,795
50 to 59	6,369	42	6.6	5,557,637	36,680
60 to 69	4,262	44	10.3	3,359,320	34,601
70 to 79	2,018	21	10.4	1,539,251	16,008
80 and over	499	5	10.0	368,148	3,681
Unknown	24	....	....	.....	....
Females:					
40 and over	24,267	299	....	17,406,242	201,946
40 to 49	8,556	43	5.0	7,224,091	36,120
50 to 59	7,095	107	15.1	5,063,844	76,464
60 to 69	5,011	86	17.2	3,162,506	54,395
70 to 79	2,637	50	19.0	1,517,143	28,826
80 and over	928	13	14.0	438,658	6,141
Unknown	40	....	....	.....	....

The notable study of defects found in men examined for military service[8] during the World War disclosed 740 cases of diabetes (0.27 per M examined). But this low rate is not surprising because most of the 2.5 million men examined were between the ages of 18 and 30 years. The sickness census taken in the course of the famous Framingham demonstration[9] in 1917 showed only 7 diabetics among 6,582 persons. But later in the same year, over 4,000 persons were given a health examination and 11 cases of diabetes were found (over 2 per M).[10] A study of illness in Dutchess County, New York,[11] in 1912 covering 12,000 persons revealed only 7 cases of diabetes

(less than 1 per M). Despite the small number surveyed, it is significant that all 7 cases were residents of towns in the county.

Periodic health examinations also throw some light on the incidence of diabetes. Unfortunately, facts from this source are limited to the incidence of glycosuria. A survey of nearly 17,000 life insurance policyholders examined by the Life Extension Institute in 1921,[12] showed an incidence of 5 cases per M with marked glycosuria (1% or more). In a later study of over 100,000 men,[13] the incidence was found to be 4 in every 1,000. A similar study of nearly 12,000 women[14] also disclosed 4 cases of marked glycosuria per M examined. In interpreting these results, the reader is cautioned that the data is limited almost entirely to adults among whom the incidence of diabetes is much higher than the population at large; that for the most part, only a single urine examination is made and that the glycosuria of 1% or more does not necessarily mean the existence of diabetes. The figures from this source, therefore, are suggestive rather than conclusive.

In view of the great variation in the incidence of recognized cases of diabetes in these several surveys, most of them limited to the East, it seems almost presumptuous to make any definite estimate of the number of cases in this country. It is our judgment, however, that a conservative estimate of the number of known cases is probably at least 2 per M, but more probably between 2.5 and 3 per M. This would place the number of known diabetics between 245,000 and 370,000, or to use round numbers, we may say that 250,000 is a conservative estimate of the number of diabetics in this country and 400,000, a generous and outside estimate. To put it in another way, 1 in every 350 to 500 persons in this country is a diabetic. This estimate excludes, of course, cases of the disease as yet undiagnosed. It is not possible to determine the number of the latter with any degree of accuracy. But there are indications that their number is fairly large. A recent survey of nearly 60,000 applications for life insurance[15] showed that 2.6 per M were rejected because sugar was present in the urine in such amounts and so persistently that it was unsafe to insure these applicants even at a substantial advance in the premiums charged. It is fairly certain that in only a few cases was the applicant aware of his condition before making his application for insurance. Another indication is the fact that in old age diabetes is often very mild and may be present a long time before symptoms of it develop. It is not improbable that undiagnosed cases are about half as numerous as the recognized cases.

The wide range of the incidence of diabetes in the various studies is significant from another point of view. It shows clearly the rapid increase in the frequency of the disease. For example, we may compare the recorded incidence in Dutchess County in 1912—less than 1 per M—and in Framingham in 1917—1.1 per M—with the figure of 4 per M in the recent state wide survey of Massachusetts described above, and the figures of 5 and 9 per M in the rural parts of New

York State. The increase in the frequency of diabetes is also indicated by data of general hospitals. The record of Bellevue and Allied Hospitals in New York is typical. In the 3-year period 1920–1922, 629 patients were treated for diabetes, but in 1928–1930, a period of the same length, the number of such cases was 1,293, or more than double the earlier figure. In the same period, the total number of patients discharged had risen from 171,267 to 217,626, an increase of only 27.1%. The ratio of diabetics to total patients rose in this interval from 3.7 to 5.9 per M.

Incidence of Diabetes in Other Countries. In Germany likewise, great interest has been shown in the incidence of diabetes and, fortunately, the data for that country are exceptionally good. A survey by Gottschalk[16] of the whole population of Stettin, a city of 268,000 inhabitants, disclosed 640 diabetics (2.37 per M)—a figure very close to the one we think most reliable for the United States. On the basis of this study, the number of diabetics has been estimated to be 150,000. Grote, however, states that the actual number may be as much as 25% higher because the working capacity of older patients is affected so little that they often do not come to the attention of physicians. The number of diabetics in Germany was estimated to be approximately 120,000 in an earlier statement by Grote. Umber placed the figure between 100,000 and 120,000, based upon his studies of the incidence of diabetes in 1916 in Berlin and its environs.

A much older study, based on the records of the Ortskrankenkasse of Leipzig[17] in 1910, a sickness insurance society with a membership of 1,000,000 men and 250,000 women, showed only 0.2 cases of diabetes per M men and 0.1 per M women. This society included no children as members, however, and was deficient in the proportion of old persons. It was made up, for the most part, of wage earners in the population. On the whole, therefore, the figures understated the incidence of the disease for a population of normal age constitution. Despite this limitation, the great disparity between the early and recent figures clearly brings out the greater frequency of cases of the disease in Germany today. The data on admissions to German general hospitals confirm this trend. Whereas in the years 1877–1879, diabetic patients constituted about 1 in every 2,500 admissions to these hospitals, the proportion increased to 1 in every 400, 30 years later. It has continued to advance so that now 1 in every 200 patients admitted is a diabetic.

The number of diabetics in England and Wales in 1923–1924 was estimated by Young and Russell[18] as about 24,000, and in all of the United Kingdom as 29,000. They based their computation upon the case mortality data of the Leipzig study, cited above. In comparison with the estimated numbers for the United States and Germany, their figures seem too low. If the average lifetime subsequent to onset of diabetes is taken at 10 years, as in one of our estimates for the United States, the annual toll of diabetes deaths, which is now

close to 6,000 in England and Wales, indicates an incidence of nearly 60,000, at present. For the United Kingdom the number would be approximately 70,000.

In Denmark, Norgaard[19] estimated the number of diabetics in 1932 to be between 5,000 and 6,000 (an incidence of 1.5 per M). The diabetic population of the country has been increasing very rapidly. In 1927 it was estimated that there were little more than 4,000 cases of the disease. Hospital data for Copenhagen also illustrate the problem admirably. In 1890 only 10 diabetics were treated in the hospitals of that city. In 1924 this figure had mounted to 608.

The number of diabetics in Sweden was estimated by Lundberg[20] at 1% of the population, or 61,000. But the figure is too high. For Switzerland the incidence in Basle was estimated by Hunziker[21] in 1918–1919, at 1.54 per M on the basis of information from food-cards required in war time. The frequency of the disease is probably greater today. Rabinowitch[22] estimates the incidence in Canada at 1% of the population, or over 100,000. This is unquestionably too high because the death rate from the disease in that country is much lower than in the United States, and its population is younger than ours. According to the latest censuses, the median age in Canada (1931) is 24.8 and in our white population (1930) is 26.9 years. It is probable that the number of known cases in Canada does not exceed 30,000. The incidence in France and other countries is unknown, as the basic data for estimating it are not available.

The Chances of Dying from Diabetes. We have already shown that the number of known diabetics in this country is probably under 400,000. This number does not, however, give us a true picture of the real importance of diabetes. Analysis of mortality data shows that over 2.5 million persons, or 2.08% of the population living in 1930 may be expected to succumb eventually to diabetes, if current death rates from the disease continue to prevail during the next generation. In our white population, diabetes may be expected to account for 2.19% of the deaths of those living in 1930; in our colored population, for 1.11%. For females, ratios are far higher than for males, thus 2.78% of the deaths of white females in the 1930 population may be expected to occur from diabetes, but only 1.61% of the deaths of males. For colored females, the expected ratio is 1.49%, but only 0.74% for colored males.

These results are obtained by computing for each age group of the population the number of persons who may be expected ultimately to die of diabetes. This can be done by the aid of a life table and of the actual proportions out of the total deaths at each age that occurred from diabetes. On the basis of these data, we can compute the proportion of all persons now of a given age—for example, 10 years—who will ultimately die of diabetes, or as we may say, the probability at age 10 of ultimately dying of diabetes.

We have computed the chances of eventually dying from the disease at successive ages of life for the two sexes separately, according to the mortality statistics of 1920 and 1930. Nothing illustrates the seriousness of the diabetes problem better than these figures. Thus, 15 white males per M born will eventually die from diabetes if the 1930 death rates continue, and 27 females per M born. Only 10 years earlier these probabilities at birth were only 13 per M for white males and 18 for white females. Thus, this probability has increased nearly $\frac{1}{6}$ for males and $\frac{1}{2}$ for females within a decade. Because of the greater increase in female mortality from diabetes, the excess of the female rate over the male reached 81% in 1930, compared with but 37% a decade earlier.

The chances of dying from diabetes vary with age. Among males there is a definite increase in the probability between birth and age 5 and a very gradual increase thereafter until well past middle life. On the basis of 1930 death rates, the maximum probability for males was reached at about age 55 when nearly 18 in each M living would be expected to die eventually from diabetes. At every age these probabilities are much higher for males on the basis of 1930 rates than in 1920.

Among females, too, there is a marked increase between birth and age 5 in the probability of dying from diabetes, and a gradual increase thereafter until past middle life. The maximum probability is, however, reached about 5 years earlier in the case of females, that is, about age 50. At that age, on the basis of 1930 death rates, 31 women per M may be expected eventually to succumb to the disease. After age 50 the probability declines at first slowly, but then sharply so that at age 80 this probability of dying from the disease is only 10 per M. Again, as in the case of males, the probabilities at every age, based on 1930 death rates, are much higher than on the basis of death rates of but a decade earlier. The excess is consistently about 50%.

It will be appreciated how far diabetes has advanced to its present importance as a factor in mortality by comparing the probabilities of ultimately dying from it with the probabilities of dying from tuberculosis (Chart I). On the basis of conditions in 1930, for women past 30, the probability of dying from diabetes is greater than from tuberculosis. In 1920 this did not occur until age 65 was reached. Among men the situation is different. The probability of dying from diabetes does not exceed that of tuberculosis until age 65, but in 1920 this did not occur until age 80. Moreover, under 1920 conditions the margin at the older ages between these probabilities for diabetes and tuberculosis was small, whereas under the mortality conditions prevailing in 1930 the probability of dying from diabetes is 50% higher than that for tuberculosis for women at 40, and more than twice as great at ages past 60. Among men, too, similar differences exist, though not at all so marked.

Let us now look into the incidence of diabetes in various geographical, racial and social groups. Here we are limited to mortality data to guide us, for either there are no data on morbidity for most of these items, or such facts as do exist are too fragmentary or specialized to be very reliable.

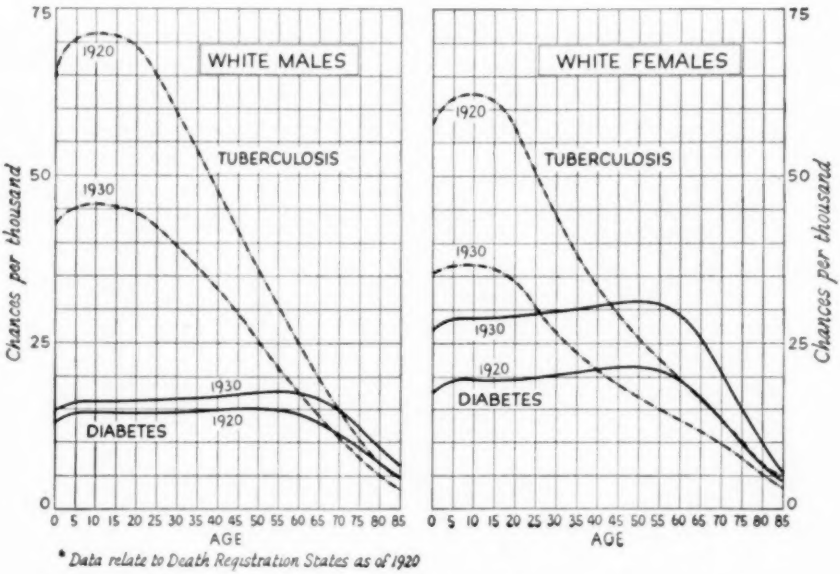

CHART I.—Chances of eventually dying from diabetes and from tuberculosis. United States* 1920 and 1930.

Urban and Rural Mortality from Diabetes. Diabetes mortality in the cities and towns is usually much higher than in the countryside. In this country† in 1929 the death rate in the urban part of the Registration States was 24.2 per 100,000, but only 14.2 in the rural areas, and for the 5 years ending in 1929, 23 and 13.8 respec-

* Data relate to Death Registration States as of 1920.

† Certain limitations of this material should be noted. (1) Available mortality data on the urban and rural populations are based upon crude death rates and thus do not take into account the differences in the sex and age composition of these populations. Correction for the factor of age would tend to increase somewhat the disparity between the urban and rural population of the country as a whole, but correction for the factor of sex would decrease it. In some parts of the country, however, the proportion of old persons is greater in the urban population; in others, it is greater in the rural population. (2) The practice of registration offices to charge deaths according to the place of occurrence also affects the death rates. Many deaths of farm dwellers from diabetes occur in cities where these people go for treatment. Investigation shows, however, that even when this has been allowed for, there is a substantial excess for the urban areas.[22] (3) Urban death rates relate to the population in communities of 10,000 or over. Towns of smaller size are classed as rural for purposes of mortality statistics and such communities contain a sizeable proportion of the "rural" population of the country—nearly 17% in 1930.

tively. Thus, for the country as a whole, the excess of the urban rate in recent years has been approximately 70%. This situation is a very general one. As Table 2 shows, in only 4 states did the death rate in the rural areas exceed that in the cities during the 2-year period 1928–1929. In these cases, an exceptionally high proportion of old persons in the rural population, or of young persons in the

TABLE 2.—DIABETES MORTALITY IN URBAN AND RURAL AREAS IN THE U. S.

Mean Death Rate Per 100,000, 1928–1929. White Persons. By State.

State.	Total.	Urban.	Rural.
Registration States	19.0	24.4	14.3
Rhode Island	26.9	26.9	27.4
New York	26.7	28.2	21.3
New Hampshire	26.0	25.6	26.4
Vermont	25.5	41.9	22.6
Maine	25.1	31.5	22.6
Illinois	23.6	26.2	19.6
New Jersey	23.3	27.3	17.7
Connecticut	23.0	24.8	17.8
Massachusetts	22.7	23.3	19.7
Pennsylvania	22.6	26.8	18.6
Maryland	22.5	27.1	16.7
Nebraska	22.3	30.7	19.7
Delaware	21.4	25.8	17.4
Indiana	21.3	23.2	19.9
Ohio	21.3	22.8	19.5
Wisconsin	20.8	25.4	17.6
Kansas	20.6	25.8	18.8
Missouri	20.6	27.0	16.3
Minnesota	20.1	22.1	19.0
Michigan	19.3	19.1	19.5
Iowa	19.1	24.5	17.0
California	19.0	21.5	15.6
Washington	18.2	23.0	14.0
Oregon	17.5	22.4	14.6
Montana	16.6	28.1	13.1
Utah	15.9	23.1	11.5
Colorado	15.5	20.0	12.6
North Dakota	15.4	29.4	14.0
Florida	14.5	19.2	12.3
Nevada*	14.4	17.1	13.7
Louisiana	13.2	24.2	7.8
Kentucky	12.6	27.5	9.0
Virginia	12.6	17.6	11.0
Idaho	12.3	27.0	10.9
Wyoming	12.2	11.1	12.4
Georgia	11.5	19.1	9.4
South Carolina	11.1	25.4	8.9
Mississippi	10.7	21.2	9.4
West Virginia	10.3	18.1	8.4
Tennessee	10.1	19.1	7.9
Alabama	9.9	18.8	7.9
New Mexico*	9.6	23.4	8.6
North Carolina	9.5	18.3	8.0
Oklahoma	9.2	14.5	7.9
Arizona	8.8	17.0	6.8
Arkansas	8.3	17.7	7.4

* Death rate in 1929, year of admission to Registration Area.

urban population, is a prime reason for the excess of the rural rates. Fluctuations due to chance may also be involved, in the case of Rhode Island, because of its very small rural population; and in Wyoming, because of its very small urban population. The higher incidence of diabetes in urban areas indicated by the mortality figures is confirmed by the Massachusetts survey of chronic illness.

In England and Wales, on the other hand, crude death rates from diabetes in the cities have been lower than in the countryside. Indeed, 1930 was the only year in the past decade when the urban death rate was higher. When, however, the death rates for both populations are adjusted for differences in age and sex composition, the rural death rate has been found consistently lower, but the difference is much smaller than in this country. In Denmark, as in the United States, the urban death rates from diabetes are much higher than in the country and have been ever since figures began to be compiled over a decade ago. In 1931 the urban death rate in that country was 18.6 per 100,000, but only 13.9 in the rural areas. The urban death rate was thus about 35% higher than the rural rate.

TABLE 3.—TRENDS IN URBAN AND RURAL MORTALITY FROM DIABETES. U. S. REGISTRATION STATES, NEW YORK, MICHIGAN AND WISCONSIN, 1900–1929.

Death Rate Per 100,000.

	U. S. Registration States.		New York.		Michigan.		Wisconsin.	
Year.	Urban.	Rural.	Urban.	Rural.	Urban.	Rural.	Urban.	Rural.
1929	24.2	14.2	27.6	23.8	18.7	20.0	24.6	15.5
1928	24.6	14.4	28.2	18.5	19.1	18.9	25.9	19.7
1927	22.4	13.3	25.0	21.5	18.0	17.2	24.2	17.0
1926	22.6	13.9	26.0	20.3	17.6	16.4	19.6	15.7
1925	21.1	13.1	24.3	19.8	18.0	16.5	20.1	18.0
1924	20.2	13.4	24.0	19.0	14.4	17.8	19.1	13.8
1923	21.9	14.3	26.2	20.9	16.9	18.2	22.8	18.2
1922	22.4	14.9	27.1	23.8	17.0	18.2	22.8	18.3
1921	20.2	13.6	23.8	20.8	13.5	19.5	18.1	17.1
1920	19.4	13.1	23.8	21.4	15.0	17.5	21.8	16.9
1919	18.0	12.2	21.4	20.6	17.7	18.1	17.0	14.4
1918	18.8	13.4	22.5	22.1	18.3	19.2	16.5	15.2
1917	20.3	14.1	23.3	23.4	19.5	19.0	16.7	16.3
1916	20.0	14.4	22.1	20.4	18.1	17.1	19.3	16.5
1915	20.1	15.4	23.6	24.6	19.3	17.4	19.1	18.0
1914	18.4	14.3	20.8	21.2	15.6	17.7	17.5	14.6
1913	17.5	13.4	19.1	18.3	15.8	16.7	17.3	14.5
1912	16.9	13.1	18.3	16.8	16.1	14.2	16.3	13.6
1911	17.0	13.0	18.9	19.5	13.5	15.0	16.5	13.5
1910	16.8	13.5	18.3	18.9	14.6	14.9	14.5	12.6
1909	15.3	12.8						
1908	14.5	12.9						
1907	15.4	12.8						
1906	14.5	12.0						
1905	14.8	13.3						
1904	14.9	13.3						
1903	13.0	12.1						
1902	11.8	11.5						
1901	12.1	10.8						
1900	11.1	10.8						

Trends of Diabetes in Urban and Rural Areas. The trend of diabetes mortality in the cities of this country has been sharply upward; in the rural part it has been much steadier. The figures for these areas (Table 3), do not, however, give a true picture of the situation, particularly in the rural population, because the states admitted to the Registration Area more recently have had lower diabetes rates than prevailed in the original states. The true situation is portrayed more accurately by the figures for diabetes mortality in New York, Michigan and Wisconsin, 3 states with large urban and rural populations. These figures, also given in Table 3, show appreciable increases in the rural death rates from diabetes since 1910, though not as great as in urban areas. Thus, in New York the rural death rate from diabetes in 1925–1929 was 10.1% higher than in 1910–1914, but the urban rate was 37.2% higher; in Wisconsin, the rise was 24.6 in the rural diabetes rate but 39.6% in the urban areas. In Michigan, the increase in the rural rates has been 13.4%, while that in the urban was 21.2%.

In England and Wales in the last decade, the trend of the diabetes rates in both urban and rural areas has been upward, especially in the former. Thus, the urban rate in 1931 was 30% higher than the rate in 1921–1922, but the rural death rate in the same period had increased by only 23%. In Denmark, too, diabetes death rates have been increasing in recent years both in the urban and rural populations. Between 1922 and 1926 following the introduction of insulin, the diabetes death rate in the cities fell sharply, but since 1926, the rate has shown a sharp and continuous advance. The 1931 death rate was the highest on record. The death rate in rural Denmark in 1931 was also higher than any previously recorded with a fairly steady rise since 1924. In comparison with the 1920 rates, there has been an increase of about 30% in the case of the cities, and of 25% in the rural areas. The figures for England and Denmark are given in Table 4.

TABLE 4.—TRENDS IN URBAN AND RURAL MORTALITY FROM DIABETES. ENGLAND AND WALES AND DENMARK, 1920–1931.

	Death rate per 100,000 England and Wales.		Death rate per 100,000 Denmark.	
Year.	Urban.	Rural.	Urban.	Rural.
1931	14.4	15.2	18.6	13.9
1930	14.3	14.2	16.8	12.7
1929	14.1	14.8	15.8	11.2
1928	12.9	14.4	15.5	11.7
1927	12.6	12.9	15.4	11.2
1926	11.3	12.8	14.3	12.1
1925	11.0	12.1	16.2	10.8
1924	10.8	12.0	16.2	9.8
1923	11.3	12.0	16.6	12.5
1922	11.7	12.8	20.2	11.2
1921	10.5	12.0	17.8	11.9
1920	9.9	10.4	14.5	11.0

Regional Differences. *United States.* In the years 1928–1929, the highest diabetes death rate in this country was registered in Rhode Island, 26.9, per 100,000 closely followed by New York with a rate of 26.7. Going back to Table 2, we find that the rates in the New England and Middle Atlantic States were high, all 9 of them being included among the 10 states with the highest rates. The states at the lower end of the scale are, for the most part, the Southern States, or the more sparsely settled states. The rates in the northeastern states are 2 to 3 times those of the Southern States. The rates used relate to white persons only. The low mortality recorded in the Southern States is, therefore, not due to the lower mortality of the large negro population. In the important agricultural states of the Middle West, the rates tend to approximate the average for the country.

These regional differences in diabetes rates in part reflect merely differences in the composition of the population. High rates prevail in states with relatively large urban populations, and low rates in those with large rural populations. This fact alone explains part of these regional differences. It is interesting and perhaps significant that there is less variability in the diabetes rates of the urban portions of the various states than in the rural rates. Thus the highest urban rates are found in Vermont (41.9), Maine (31.5) and Nebraska (30.7). In few states are the urban rates much below 20. In the rural population, on the other hand, the rates vary from less than 8 in 6 states to 20 or over in 5 states. The rates in rural regions tend to be especially low in the south. There is, it is true, some association between the level of the urban and rural rates in the individual states, but the relationship is not at all consistent. The reader is again cautioned that these rates are not adjusted to eliminate age and sex differentials in these various states and consequently the possibility of differences from these sources must be kept in mind.

Europe. Diabetes mortality tends to be high in the countries of northern and western Europe and low in the southern countries. In the Netherlands, the rate—17.7 in 1931—is the highest on that continent. Belgium and Denmark suffered the next highest rates, 15.9 per 100,000 in both cases. The lowest rates for European countries for which we have mortality records, are found in Spain, Italy and Czechoslovakia and are only about half that of the Netherlands. The rates for European countries may be found in Table 2 of our first paper.[24]

Presumably the incidence of diabetes varies in much the same way, but of this we cannot be certain. Unfortunately only for the countries of Northern Europe do we have any estimates of incidence, and even these are only approximations. Again, we are dealing with crude mortality rates and data to adjust them for sex and age differences in the populations of these countries are not generally available. In part, at least, the differences are explicable on the

basis of these factors alone. For, recent figures on age distribution of a few countries indicate that the level of the diabetes mortality rate in these countries tends to reflect the proportion of old persons. To some extent, also, the differences in the rates reflect variations in methods of classifying causes of death. This factor is not a measurable one, but fortunately in most countries of Northern Europe at least, death registration is of a high order and such differences* as exist affect the rates from diabetes less than most causes of death.

Racial and National Differences. *General.* There is in a broad sense, some correspondence between regional, national and racial areas. The regional data just presented should, therefore, indicate that higher diabetes death rates prevail among Teutonic peoples than among Latins and Slavs. Our data on the last named are, however, most deficient. One cannot do more than make this broad generalization because pure racial lines are the exception rather than the rule; so great has been the admixture of the various European Stocks. The diabetes mortality of the colored races, as our first paper has shown, is lower than for the white. Mills,[25] who resided in China for 2 years, observed that among the Chinese diabetes was relatively infrequent and mild in character. He also quotes others on the rarity and mildness of the disease in Japan, the Philippines, India, the Sudan, West Africa and in Venezuela. In the East, it is reported with frequency only among the wealthy and leisured classes; and the adoption of western diets is given as a possible reason for it.

United States. Differences in diabetes mortality exist among the many racial stocks in this country. The facts are not clear-cut, however, because the data are based upon national origin, which is often not at all synonymous with racial origin. The material is also rather limited. The only facts of value are on mortality according to country of birth of mother for 1920 and of the foreign born in 1910. Only in New York State and in Pennsylvania were there sufficient persons in the several nationality groups upon which comparisons could be made. Further difficulty arose from the rearrangement of national boundaries as a result of the World War. Despite these difficulties, however, we find a surprising degree of agreement in the studies so far made. In general, diabetes death rates of those of native birth in these two large states were found to be average or even lower. In New York State, persons of Russian origin or Austro-Hungarian origin (most of whom were Jews) had high death rates from diabetes. In Pennsylvania, on the other hand,

* They are of two origins: (1) Varying procedure in the assignment of the determining cause of death where two or more are stated; (2) the proportion of deaths in which the certifying physician has reported only the terminal conditions, or stated the cause in indefinite, or unsatisfactory terms (senility, "sudden" death, hypostatic pneumonia, dropsy, etc.). Some registration offices try to ascertain the true cause of death in such cases.

the diabetes rates among persons of these origins were lower than in New York State, especially as regards Austria-Hungary. These differences were probably due to the smaller proportion of Jews among persons of these national origins in that state than in New York. Persons of German origin and of Irish origin also had average or above average rates. In contrast, the mortality for persons of Italian parentage was extremely low in both states.

A surprising feature of these experiences is the high mortality found among the Irish. It has been generally assumed that the diabetes rate in this group is low. The basis for this assumption is probably the low diabetes rate prevailing in Ireland and the high mortality which the Irish suffer from tuberculosis. That high tuberculosis rates are associated with low diabetes rates and *vice versa* is an impression very general but not altogether well founded. The reason for the high diabetes mortality of the Irish here is not far to seek. The level of well-being and prosperity among the Irish in this country is far higher than in Ireland itself. Another item—not a negligible one—is that at the time covered in these studies, a disproportionate number of the Irish engaged in the liquor business, an occupation in which, as we shall see later, diabetes mortality is exceptionally heavy.

Table 5 gives detailed figures for Pennsylvania and New York in 1910. These relate solely to the native born and the foreign born. Because of the age of the material, the authors present it with some hesitation, but unfortunately no better data exist. Data for 1920 are not reproduced here because the Census Bureau did not consider the facts on persons of Russian and Austrian maternal parentage sufficiently reliable.

TABLE 5.—DIABETES AND NATIONALITY.

Standardized Death Rates per 100,000 White Persons in New York State and Pennsylvania by Country of Birth, 1910. By Sex for Specified Ages.

Sex, age groups.	United States.		Austria-Hungary.		England, Scotland, and Wales.		Germany.		Ireland.		Italy.		Russia.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
NEW YORK STATE:														
All ages	15.4	16.1	15.0	32.7	15.1	18.8	22.1	28.9	18.4	28.7	4.1	8.0	18.3	26.4
25 to 64	21.1	21.6	16.2	29.7	19.5	29.3	29.8	41.6	30.8	46.2	9.4	14.1	17.8	35.9
PENNSYLVANIA:														
All ages	11.4	14.5	0.6	7.9*	13.9	19.2	14.3	20.3	14.1	19.6	2.5*	10.4*	9.2*	15.8*
25 to 64	14.1	18.7	1.3	17.4*	7.8	33.3	18.6	31.2	24.8	27.2	5.8*	18.1*	5.8*	19.2*

M. = Male. F. = Female.
* Based on less than 10 deaths from diabetes.

Particular interest attaches to the diabetes mortality of the Jews. Observations made all over the world indicate a greater frequency of diabetes among them, as compared with other peoples. Physicians treating large numbers of diabetics have frequently commented

upon the disproportionate number of Jewish patients. The high incidence of diabetes in Jews is observed in the facts on mortality of foreign race stocks in this country. Supporting data on this subject are abundant but often of uncertain quality. Probably the best material on the subject is contained in the Jewish Communal Survey of Greater New York.[26] This is reproduced in Table 6, which compares the diabetes mortality of the Jewish population in certain areas of the city in 1925, with that of the total population of the city. It is interesting to note that the crude rate of the Jews is little higher than that of the general population because they are a very young group. When the rates are adjusted for age, however, the Jewish rate is 50% higher than the general city rate. The lower rates of the Jews at the younger ages may simply be due to chance because the number of deaths from diabetes in that year was small. It may possibly be due to the better treatment obtained by young Jewish diabetics. Past 45, the rates for Jews are higher and in old age are double the general rate.

TABLE 6.—DIABETES AMONG JEWS. DEATH RATES PER 100,000. JEWISH AND TOTAL POPULATION IN NEW YORK CITY COMPARED, 1925.

Age groups.	Jewish population.	Total population.
All ages, standardized	35.8	24.4
crude	24.7	22.3
Under 25	0.4*	0.9
25 to 34	2.2*	2.2
35 to 44	7.2	8.1
45 to 54	60.2	39.2
55 to 64	170.4	134.2
65 to 74	360.1	239.4
75 and over	506.7	232.1

* Based on less than 10 deaths.

The high incidence of diabetes among Jews was also shown by Bolduan and Weiner[27] who compared the proportion of deaths from diabetes to the total deaths among Jews and non-Jews in New York City in 1931. Their material consisted of the death certificates of persons buried in strictly sectarian cemeteries. The proportion of diabetes deaths at all ages (Table 7) was nearly 80% higher among Jews than non-Jews. This excess was found to exist both among males and females, but was largely restricted to the more advanced ages. Under 45 there was only a slight excess in the proportion of diabetes deaths among Jews. It is interesting to note that the proportion of such deaths among Jewish women between ages 55 and 64 reached the amazing figure of 11.5%. Somewhat greater differences in diabetes incidence between Jews and non-Jews were found by DePorte[28] in a similar analysis of death records for 1925 in New York State, outside of New York City. Similar results were obtained in earlier studies of mortality for Boston in 1895 to 1913, by Morrison;[29] for Budapest in 1902 to 1907, by Auerbach;[30] for New York City in

1900, by Stern;[31] for Frankfurt-A. M. in 1872 to 1890, by Wallach;[32] and in the United States in 1890, by Billings.[33] It should be pointed out that differences in the total death rates of Jews and non-Jews have a serious effect on the accuracy of comparisons of this type.* Fortunately, the differences in the proportions of diabetes deaths among Jews and non-Jews are so great that we may safely accept the figures as good evidence of difference though not as accurate measures of their degree.

TABLE 7.—DIABETES AMONG JEWS. PER CENT DIABETES DEATHS OF TOTAL DEATHS AMONG JEWS AND NON-JEWS. BY SEX AND AGE, NEW YORK CITY, 1931.

	Per cent diabetes deaths of total deaths.			
	Males.		Females.	
Age groups.	Jewish.	Non-Jewish.	Jewish.	Non-Jewish.
All ages	2.5	1.4	6.3	3.6
Under 25	0.2*	0.1*	0.6*	0.2†
25 to 44	0.9*	0.8	1.2	1.1
45 to 54	2.3	1.6	8.1	5.4
55 to 64	4.0	2.0	11.5	6.6
65 to 74	3.7	2.7	8.3	5.5
75 and over	2.3	1.5	4.3	2.5

The lower than average diabetes mortality of most of the colored groups in this country was brought out in our first paper. This applies to negroes, Indians and Japanese. The Chinese in this country have a high rate, but this group is made up chiefly of adult men. In China itself, the disease is relatively uncommon, according to Mills'[34] observation, cited above. On the other hand, he has also observed from his contact with Chinese students, that on European diets they easily develop boils and a mild glycosuria. These factors and the abnormal living conditions of the Chinese in this country probably indicate the reasons for their high diabetes mortality here.

Social and Economic Differences in Diabetes Incidence. Diabetes mortality differs in the various strata of society. The latest study of this subject relates to males in England and Wales in the years 1921 to 1923.[35] The special report of the Registrar-General on mortality according to social classes classified the male population into 5 main groups as follows: Class I, professions and the higher ranks of business life; Class II, farm owners, retail merchants, clerical workers, teachers and the like; Class III, skilled workers, sales clerks, etc.; Class IV, semiskilled workers, including agricultural laborers; and Class V, unskilled workers.

The highest diabetes death rate was recorded in Class II and the next highest, in Class I. With this exception, diabetes mortality is highest in the upper classes and decreases progressively with each successive grade of social standing. Thus, the mortality in Class I was 25% above average for all occupied and retired civilians, and

* If, for example, at a stated age, the total death rate of one group is 20% lower than that of the other, identical diabetes rates would yield a proportion of diabetes deaths 25% higher in the former than in the latter.

† Based on less than 10 deaths.

in Class II, 45% above, but in Class III nearly 10% below the average, in Class IV, nearly 25% below and in Class V, nearly 35% below. The mortality in Class II is well over twice as high as that in the lowest groups in the social scale. These findings are in general agreement with the earlier English study[36] along these lines (1910–1912).

The differences in the diabetes mortality in the various social classes vary with age. Generally speaking the differences are least in younger persons and most in old age. The mortality in Class II is highest, but past 65, the rank goes to Class I. In old age, the mortality in these two upper social classes is from 4 to 5 times as high as among unskilled workers. Data from the Registrar-General's report are given in Table 8.

TABLE 8.—DIABETES AND SOCIAL.

Death Rates per 100,000 Among Males, Aged 16 and Over, Classified According to Social Status and the Ratio of the Rate in Each Class to that of all Occupied and Retired Civilians by Age. England and Wales, 1921 to 1923.

Age group.	Death rate per 100,000.						Per cent of death rate of all occupied and retired civilians.				
	All occupied and retired civilians.	Social class.					Social class.				
		I.	II.	III.	IV.	V.	I.	II.	III.	IV.	V.
All ages: 20 to 65*	12.2	15.2	17.7	11.2	9.2	8.1	124.6	145.1	91.8	75.4	66.4
16 to 19	3.3	2.6	2.3	3.8	3.2	2.8	78.8	69.7	115.2	97.0	84.8
20 to 24	4.5	4.3	5.1	4.5	4.3	4.2	95.6	113.3	100.0	95.6	93.3
25 to 34	5.5	6.3	7.1	5.3	4.7	5.2	114.5	129.1	96.4	85.5	94.5
35 to 44	6.7	4.7	8.0	6.6	6.6	5.2	70.1	119.4	98.5	98.5	77.6
45 to 54	12.8	19.0	19.3	11.5	8.9	10.7	148.4	150.8	89.8	69.5	83.6
55 to 64	32.4	46.8	55.1	30.4	21.4	14.5	144.4	170.1	93.8	66.0	44.8
65 to 69	65.3	153.0	114.3	61.2	36.2	26.5	234.3	175.0	93.7	55.4	40.6
70 and over	99.7	203.9	177.2	71.7	56.4	45.7	204.5	177.7	71.9	56.6	45.8

* Standardized.

Diabetes and Occupation. It is to be regretted that no authentic data are available on the incidence of diabetes in various occupations. The reports of the Registrar-General give the most instructive information but are based on mortality. Table 9 indicates why the mortality in the two upper social classes is higher than in the working classes; for among occupations with high rates are auctioneers, commercial travellers, farm owners, physicians, teachers, office workers and certain types of tradesmen. The persons following these occupations are classified in the two upper social classes.

The most striking feature of the table, however, is that the highest mortality is recorded for persons engaged in occupations relating to the distribution and serving of food and drink. Thus, the mortality of inn- and hotelkeepers and publicans is 285% of the average, the highest recorded for any large occupational group. Not far behind are to be found both sales clerks and owners of businesses for the sale of meat, fish, grocery and provisions. Bakers and pastry

TABLE 9.—DIABETES AND OCCUPATION. STANDARDIZED MORTALITY AMONG MALES AGED 20 TO 65 IN SPECIFIED OCCUPATIONS† COMPARED WITH THAT OF ALL OCCUPIED AND RETIRED CIVILIAN MALES TAKEN AS 100. ENGLAND AND WALES, 1921–1923.

High mortality.		Average mortality.		Low mortality.	
Occupation and social class.	Mortality ratio.	Occupation and social class.	Mortality ratio.	Occupation and social class.	Mortality ratio.
Inn, hotelkeepers, publicans (II)	285	Railway clerks (II)	111	Coal mine—underground workers, not hewers or superintending staff (IV)	85
Woolen and worsted weavers* (III)	257	Civil service officials and clerks (II)	107	Carpenters, coach builders, pattern makers and similar occupations (III)	82
Auctioneers, appraisers, valuers (I)	220	Bakers and pastry cooks (III)	102	Proprietors, etc., of businesses for the sale of textiles and clothing (II)	80
Salesmen, etc., in businesses for sale of fish, meat, green grocery, milk (III)	203	Drivers of horse-drawn vehicles (IV)	101	General and undefined laborers (V)	79
Salesmen, etc., in businesses for the sale of grocery and provisions (III)	190	Tailors; tailors' pressers and machinists	101	Coal mine—workers above ground, not superintending staff (IV)	79
Proprietors, etc., of businesses for sale of fish, meat, green grocery, milk (II)	183	ALL OCCUPIED AND RETIRED MALES (= AVERAGE)	100	Clergymen (Anglican Church) (I)	78
Proprietors, etc., of businesses for the sale of grocery and provisions (II)	177	Insurance agents and canvassers (III)	99	Machine tool workers and metal spinners* (III, IV)	76
Dye mixers and dyers* (IV)	160	Warehousemen (II)	96	Gardeners and their laborers (III, V)	65
Commercial travellers (II)	159	Coal mine—persons conveying material to the shaft (IV)	90	Coal miners—not superintending staff (III, IV)	64
Registered medical practitioners (I)	156	Fitters, toolsetters, millwrights, and similar occupations (III)	89	Agricultural laborers (including shepherds) (IV)	60
Proprietors and managers of wholesale or retail dealing businesses (II)	148	Painters and decorators (III)	89	Bricklayers (III)	60
Salesmen and shop assistants (III)	146	Drivers of motor vehicles and steam wagons (III)	88	Contractors' laborers; navvies (V)	60
Railway signalmen (III)	142	Coal mine—other workers below ground (IV)	86	Other dock laborers* (V)	56
Locomotive engine drivers, firemen, cleaners (III)	134			Coal mine—subordinate superintending staff* (III)	56
Farmers and their relatives (II)	131			Coal mine—hewers and getters (III)	46
Railway officials, station masters, etc. (II)	127			Building-trade laborers (V)	43
Employers, managers in building, etc., trades; clerks of works (II)	121			Farm bailiffs and foremen* (III)	29
Smiths and skilled forge workers (III)	121				
Railway porters and lampmen (IV)	121				
Clerks (not civil service or local authority); typists (II)	118				
Stationary engine and crane drivers (III)	117				
Teachers (not music teachers) (II)	116				
Local authority officials and clerks (II)	116				

* Occupational groups with 15–24 deaths from diabetes. All other groups had 25 or more deaths.

† Mortalities are classified by size of mortality ratio as follows: High, 115 or more; low, 85 or less; average, 84–114. Figures in parentheses indicate the social class in which the occupational group is classified.

cooks surprisingly have a diabetes mortality only a little higher than average. Other groups with significantly high rates are various types of railway workers.

At the other end of the scale, we find consistently that workers doing hard manual labor experience the minimum rates from diabetes. For example, the mortality of building-trade laborers is only 43% of the average for all occupied persons; of coal-mine hewers and getters, only 46%; of dock laborers, 56%; and of contractors' laborers and navvies, only 60%. One group with a low mortality which does not fit in with this general picture is that of clergymen belonging to the Anglican Church who have a mortality 22% better than the average for all occupied persons.

American data tend to confirm these results. The only available source in this country is the mortality experience of the Industrial Department of the Metropolitan Life Insurance Company.[37] Most of the men in this experience are wage earners and the representation of persons in the highest economic grades is small. Analysis of the deaths during 1922–1924 revealed a high diabetes mortality among merchants and storekeepers, office workers and also among saloonkeepers and certain types of railway workers. Laborers, miners and farm workers had a low mortality. Table 10 gives the figures for the larger occupational groups in this experience.

TABLE 10.—DIABETES AND OCCUPATION. OCCUPATIONS IN ORDER OF RANK OF MORTALITY FROM DIABETES.* METROPOLITAN LIFE INSURANCE COMPANY, INDUSTRIAL DEPARTMENT, 1922–1924.

Occupation.	Standardized relative index, ages 15 to 64†
HIGH DIABETES MORTALITY (INDEX 115 OR OVER)	
Merchants and storekeepers	204
Tailors and other clothing workers	185
Saloonkeepers and bartenders	157
Railway enginemen and trainmen	154
Electricians	140
Store clerks and salesmen	137
Watchmen and guards	125
Clerks, bookkeepers and office assistants	121
Stationary engineers and firemen	118
AVERAGE DIABETES MORTALITY (INDEX 86 TO 114)	
Machinists	107
Iron and steel-mill workers	107
ALL OCCUPATIONS (EXCLUDING RETIRED)	100
Railway track and yard workers	97
Plumbers, gasfitters, and steamfitters	96
Textile (except cordage, hemp, dyeing, and finishing) millworkers	91
LOW DIABETES MORTALITY (INDEX 85 OR LESS)	
Teamsters and drivers	84
Furniture and other woodworkers	81
Farmers and farm laborers	77
Laborers	68
Janitors and building employees	68
Painters, paperhangers, and varnishers	61
Carpenters	59
Coalminers (underground)	51

* Occupations with less than 15 deaths excluded except where the mortality is very high or low.

† For explanation of this term see original Ref. 37.

The Effects of War and Economic Crises on Diabetes. The period of the World War was marked by drastic declines in diabetes mortality. Three features of especial significance stand out in this War experience: (1) these declines were not immediate; (2) they did not end until 2 or 3 years after the close of the War; and (3) they were not limited to the fighting nations. In England, for example, diabetes rates actually increased in the early War years. In Germany, if we may take Berlin as typical, the declines in the first 2 years were no greater than pre-War fluctuations, and, likewise in France as represented in the data for Paris. Subsequently, the rates fell sharply, usually beginning in 1917, and continued to fall up to 1920. If we compare the 1914–1916 levels with those for 1917–1920, we find that in England, the decline amounted to 17%; Berlin, 42%; and Paris, 21%. Even in the United States which did not enter the War until 1917, the decline was 5%. Neutral countries experienced declines in diabetes mortality somewhat less drastic as, for example, 6% in Holland and 10% in Sweden and Switzerland.

These great changes in the diabetes death rates during and after the War are significant. To a limited extent, so far as the warring nations are concerned, part of this fall may have been fictitious. Because of the diversion of physicians into military service and the consequent restriction on medical care available to civilians many cases of diabetes were probably not diagnosed. Counter-balancing this situation in some degree, however, is the probability that known diabetics did not receive adequate care. This would tend to increase their death rate. These items certainly did not hold true for neutral countries in which the diabetes rates also fell. Both the warring nations of Europe and the neighboring neutral countries were subjected to sharply restricted food supplies and a consequent reduction in per capita food consumption. It is probable that this in part explains the fall in the rates during the War.

Economic crises might also be expected to result in sharp declines in diabetes mortality, because they are accompanied by drastic reductions in the incomes of large numbers of people. Examination of the data for the present century do not, however, show this effect in any marked degree. The crisis of 1907 is not reflected in the course of the diabetes death rate in this country or in England. During 1912–1915 the rate in this country continued to rise although there was a sharp decline in business. The year 1921 which witnessed a serious economic upheaval was marked by an increase in diabetes death rates almost everywhere. Again, since 1929, the rates from the disease have been going up in almost every country despite the severe world-wide depression. This result may represent the working of several forces. Depressions are usually accompanied by declines in commodity prices and, unless acute shortage exists, the prices of foodstuffs drop as rapidly as the rest. Conse-

quently, the fall in consumption of food is not as great as one would otherwise expect, particularly since there is a tendency for a greater proportion of the family income to be spent on food. Moreover, depressions actually bring improvement to the economic position of one large group—namely, those with relatively fixed incomes. Another factor in the situation is the neglect to secure proper medical attendance which results in some premature deaths of sufferers from the disease, and this also keeps the rate from falling for a time.

Sugar Consumption in Relation to Diabetes. Much has been written on this subject, but, as the earlier writings of one of us[38] have stated, the relationship is of doubtful validity. Table 11, largely reproduced from Mills'[39] article, gives the facts on sugar consumption during 1923–1928 and the diabetes death rates in several countries in 1927. He concludes that no direct relationship between sugar consumption and diabetic deaths is shown. Some countries with a high sugar consumption (Hawaii, Argentina, Cuba) had a relatively low diabetic death rate, while some with a high rate from diabetes (Netherlands and the Union of South Africa) had a low sugar consumption. Of the 13 countries highest in consumption of sugar, however, 11 were among the 13 highest in the death rate from diabetes.

TABLE 11.—DIABETES MORTALITY AND SUGAR CONSUMPTION IN VARIOUS COUNTRIES. 1923–1928.

Country.	Diabetes death rate per 100,000 in 1927.	Sugar consumption—kilograms per capita.				
		1927–1928.	1926–1927.	1925–1926.	1924–1925.	1923–1924.
United States	17.5	49.6	51.3	52.2	52.5	49.2
Netherlands	16.3	30.0	26.3	28.7	28.6	26.8
New Zealand	13.7	29.5	34.1	37.7	50.0	46.0
Belgium	13.3	26.4	24.4	24.6	24.9	21.9
Australia	13.1	58.0	58.2	58.3	58.7	59.9
Denmark	13.0	51.7	48.6	53.8	49.7	48.2
England and Wales*	12.6	44.8	41.1	41.2	40.6	38.4
Sweden	12.0	37.7	35.9	37.0	37.1	33.8
Canada	11.1	40.8	40.3	41.4	41.9	40.0
Norway	10.5	31.4	30.4	27.0	28.0	23.0
Switzerland	10.3	42.5	34.3	39.7	36.3	36.8
Spain	9.3	12.2	11.9	10.8	10.8	10.5
Hawaii	8.5	55.1	55.0	55.0	54.7	54.4
Italy	7.1	9.1	8.9	8.9	8.4	8.7
Czechoslovakia	6.3	27.0	25.7	28.6	27.6	25.8
Cuba	5.1†	44.3	44.9	44.0	35.6	33.1
Chile	3.5	....	....	....	20.2	25.0
Japan	3.5	....	12.7	12.4	....	....

* Sugar consumption for Great Britain.
† 1926.

Also no constant relationship between sugar consumption and the diabetic death rate was found. In some with a steady increase in sugar consumption for many years, there has been a recent decline in diabetic deaths (*e. g.*, Norway and Australia). New Zealand with

a marked decline in sugar consumption showed little change in the diabetic death rate. Hawaii, with a steady high consumption of sugar showed a considerable increase in diabetes. In the United States, the consumption of sugar has been constant for several years, but diabetes is increasing.

The authors agree with Mills that the increase in sugar consumption is not the cause of the increase in the diabetes death rate. The consumption of sugar may, however, be a rough index of nutrition or the total food consumed and to that extent accounts for whatever degree of association there is between sugar consumption and diabetes mortality. For in northern countries where sugar consumption is high, food requirements are higher than in warmer climates, and the greater use of sugar in the former is undoubtedly due to its cheapness as a source of energy for body needs. In some cases, of course, this does not hold, notably for countries which specialize in the production of sugar, namely, Cuba, Puerto Rico, Hawaii and the Philippines.

Summary. Consideration of the available material on incidence of diabetes and the factors underlying variations in its frequency reveals these significant facts.

1. The number of known diabetics in this country is probably between 300,000 and 400,000. This estimate takes into account current diabetes mortality, the duration of life of diabetics, and the incidence of diabetes recorded in the various sickness surveys.

2. A large increase in the incidence of diabetes is indicated by comparison of earlier surveys with recent ones, and also by hospital statistics.

3. The incidence of diabetes abroad seems to be lower than in this country. Here the case incidence is about $2\frac{1}{2}$ to 3 per M, compared to $1\frac{1}{2}$ to $2\frac{1}{2}$ in the various countries of western Europe. The number of diabetics in Germany is estimated as 100,000–150,000 and in England as 50,000–75,000. Estimates for the other large countries cannot be made, because data necessary for computing them are not available.

4. Mortality statistics show that $2\frac{1}{2}$ million persons (2.08% of the present population) may be expected ultimately to succumb to the disease. The chances of eventually dying from diabetes are nearly twice as high for females as for males, and are higher for white persons than colored persons.

5. Diabetes is more prevalent and seems to be increasing faster in urban areas than in rural ones.

6. In this country, the northeastern states have a much higher diabetes death rate than those in the south. Average rates prevail in the middle west and on the Pacific Coast. This variation is greater in the rural than in the urban population.

7. In Europe diabetes rates are relatively high in the north and west and low in the south.

8. The Teutonic peoples suffer more frequently from diabetes than the Latins. The data on Czechoslovakia, if typical, indicate a low diabetes rate among the Slavic peoples. National and racial tendencies in this country conform largely to those abroad, except among the Irish, who, in Ireland, have a very low diabetes rate, but a high rate in this country.

9. Recent studies of mortality in New York bring out clearly the excessive frequency of diabetes in Jews and confirm earlier clinical observations. This finding does not seem to apply to young Jews. Among the older ones, the incidence is probably 1½ to twice the average.

10. Diabetes is more frequent in the higher than in the lower social classes.

11. The employing and professional groups tend to have high diabetes rates. This is also true of those who sell or serve food and drink. Diabetes is least frequently found in persons engaging in occupations requiring hard manual labor.

12. Long sustained wars result in decreases in the diabetes rate, largely as a consequence of the reduction of food supplies available to civilians. For a variety of reasons the effect of economic crises is not altogether clear-cut, but in any case, it is less direct and less influential than the effect of war conditions.

13. Sugar consumption in itself is not an important factor in the diabetes rate, nor in the increasing incidence of the disease.

In the judgment of the authors the several external factors influencing the incidence of diabetes, which are the subject of the present article, depend upon a very few basic forces. We shall next discuss what these are and the way in which they operate.

REFERENCES.

1. Bigelow, G. H., and Lombard, H. L.: Cancer and Other Chronic Diseases in Massachusetts, Houghton Mifflin Company, Boston and New York, 1933.
2. DePorte, J. V.: New York State J. Med., 1929, **29**, 1310.
3. DePorte, J. V.: J. Am. Med. Assn., 1929, **92**, 522.
4. Jarrett, M. C.: Chronic Illness in New York City, Vol. 1, Columbia University Press, New York, 1933, p. 201.
5. Lombard, H. L.: Am. J. Pub. Health, 1928, **18**, 1089.
6. Lombard, H. L., and Scammon, C. L.: New England J. Med., 1928, **198**, 625.
7. Sydenstricker, E.: Public Health Repts., 1926, **41**, 2069.
8. Love, A. G., and Davenport, C. B.: Defects Found in Drafted Men, Government Printing Office, Washington, 1920, p. 109.
9. The Sickness Census, Framingham Monograph No. 2, Framingham, 1918, pp. 12 and 14.
10. Medical Examination Campaign, Framingham Monograph No. 4, Framingham, 1918, pp. 13 and 16.
11. Marsh, E. H.: Med. Times, 1922, **50**, 253.
12. Dublin, L. I., Fisk, E. L., and Kopf, E. W.: Am. J. Med. Sci., 1925, **170**, 576.
13. Sydenstricker, E., and Britten, R. H.: Am. J. Hyg., 1930, **11**, 73.
14. Britten, R. H.: Ibid., 1931, **13**, 741.
15. Medical Impairments and Mortality, Metropolitan Life Insurance Company, 1933.
16. Grote, L. R.: J. State Med., 1931, **39**, 732 (contains references to Gottschalk and Umber).

17. Krankheits-und Sterblichkeitverhältnisse in der Ortskrankenkasse für Leipzig und Umgegend, Kaiserliches Statistisches Amt, Berlin, 1910, **2**, Part A, p. 13.
18. Young, M., and Russell, W. T.: Quart. J. Med., 1926, **20**, 84.
19. Norgaard, A.: Brit. Med. J., 1933, **1**, 1.
20. Lyon, E.: Sozial-medizinische Grundlagen der Zuckerkrankheit, S. Karger, Berlin, 1932, p. 6.
21. Ibid.
22. Rabinowitch, I. M.: Diabetes Mellitus, a Handbook of Simplified Methods of Diagnosis and Treatment, Macmillan Company, Toronto, 1933, p. 10.
23. Dorn, H. F.: J. Am. Statist. Assn., 1932, **27**, 401.
24. Joslin, E. P., Dublin, L. I., and Marks, H. H.: Am. J. Med. Sci., 1933, **186**, 754.
25. Mills, C. A.: Arch. Int. Med., 1930, **46**, 569.
26. Jewish Communal Survey of Greater New York, First Section: Studies in the New York Jewish Population, Bureau of Jewish Social Research, 1928.
27. Bolduan, C., and Weiner, L.: New England J. Med., 1933, **208**, 407.
28. DePorte, J. V.: New York State J. Med., 1928, **28**, 1155
29. Morrison, H.: Boston Med. and Surg. J., 1916, **175**, 54.
30. Auerbach, E.: Ztschr. Demogr. Stat. Juden, 1908, **4**, 164.
31. Stern, H.: Med. Rec., 1900, **58**, 766.
32. Wallach: Deutsch. med. Wchnschr., 1893, **19**, 779.
33. Billings, J. S.: Vital Statistics of the Jews in the United States, Bulletin No. 19, U. S. Census Bureau, 1890.
34. Mills, op. cit., p. 569.
35. The Registrar-General's Decennial Supplement, England and Wales, 1921. Part II, Occupational Mortality, Fertility and Infant Mortality, London, His Majesty's Stationery Office, 1927.
36. Supplement to the Seventy-fifth Annual Report of the Registrar-General for England and Wales. Part IV. Mortality of Men in Certain Occupations in the 3 Years 1910, 1911 and 1912, London, His Majesty's Stationery Office.
37. Dublin, L. I., and Vane, R. J., Jr.: Causes of Death by Occupation, Bull. U. S. Bureau of Labor Statistics, No. 507.
38. Joslin, E. P.: The Treatment of Diabetes Mellitus, 4th Edition, Lea & Febiger Philadelphia, 1928, p. 165.
39. Mills, C. A.: Arch. Int. Med., 1930, **46**, 582.

THE EFFECT OF ADRENALIN ON THE ALIMENTARY LIPEMIA OF DIABETICS.*

By Maurice Sullivan, M.D.,
INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY,
AND
Paul Cameron, M.D.,
RESIDENT IN MEDICINE, TOURO INFIRMARY,
NEW ORLEANS.

(From the Department of Medicine, School of Medicine, Tulane University, and the Diabetic Clinic, Touro Infirmary.)

The utilization of ingested fat in health and disease and what regulates this utilization has never been satisfactorily explained. Numerous investigators have demonstrated the rôle of adrenalin in carbohydrate metabolism and its antagonistic action to insulin. As insulin lowers blood lipoids,[1, 2, 3, 4, 5, 6, 7] as well as blood sugar,

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it is important to determine whether adrenalin, which causes an increase in blood sugar, would cause an increase in blood lipoids, and whether adrenalin would counteract the action of insulin on lipemia if the two hormones exerted their influence simultaneously.

With a fat method essentially that of Steward and White,[8] Himwich and Spiers[9] demonstrated a parallel rise of blood sugar and blood fats following the injection of adrenalin into animals, also an apparent equalizing or counteracting force of insulin on this adrenalin effect. Then Himwich and Fulton[10] showed that after noxious stimulation of animals calculated to cause emotional excitation and stress thereby presumably increasing their secretion of adrenalin, there was a rise in the blood fats as well as the blood sugar. Koskoff and Dusser de Barenne,[11] using the Stewart and White method, found that stimulation of the central end of the sciatic nerve in an anesthetized cat caused a reflex hyperlipemia. These findings Long and Venning[12, 13] disputed because they discovered in the Stewart and White method and its modification two sources of error: (1) During the saponification of alcohol-ether extract of plasma the glucose present breaks down the complex organic acids which are titrated as fatty acids; (2) phosphoric acid is liberated from the hydrolysis of phospholipoids and is titrated as fatty acid. Thus the alleged rise in blood fats after adrenalin was due to the increased blood sugar in the faulty method employed. With the Stoddard and Drury[14] method which is free from these two objections, Long and Venning found no increase in blood fats after adrenalin injections, whereas the same samples of blood tested with the Stewart-White method showed a decided "increase in lipoids."

Page and Pasternak[15] gave normal dogs 0.3 mg. of adrenalin every 15 minutes and 4 hours after the first injection noted a diminution of cholesterol, phosphorus, fatty acids and total fat in serum, an increase of the same in the liver, and a reduction of the same in the kidneys. There was also found a reduction of phosphatids with an increase of cholesterol in the brain and in the heart and slight reduction of the fatty acids (unsaturated), a reduction of phosphatid and cholesterol and a slight reduction of the unsaturated fats. In dogs with hyperlipemia they obtained similar findings. They concluded that although the mechanisms of insulin and adrenalin actions were different, their effects on blood fat were the same.

Using the Bang method Fleisch[16] found that intravenous injections of 0.1 to 1 mg. of adrenalin in animals produced during 24 hours a sinking of the blood-fat content of 17 to 30 per cent. Large doses of 3 to 6 mg. subcutaneously caused in the first or second day an intensive increase in the blood fat (2 to 4 fold). This increase ordinarily passed in 24 hours. Very small doses up to 0.1 had no certain effect. Raab[17] found that small doses of adrenalin (0.1 to 1 mg.) caused a sinking of the blood-fats. Bornstren and Müller[18]

demonstrated a strong reduction of total and neutral fat in normal dogs after adrenalin.

Analyzing the findings of these different investigators it is noted that although Long and Venning found no change in blood fats after adrenalin and Fleisch obtained an increase after a massive dose, the findings of Page and Pasternak, of Fleisch, of Raab, and of Bornstren and Müller are in agreement, namely, after small or moderate doses of adrenalin there is a decrease in blood fats. As a step toward the ultimate understanding of the complexities of fat metabolism this fact is significant. It would appear, however, that in a problem in which utilization of foodstuff (fat) is a paramount issue, the obvious approach would have been the study of subjects in the absorptive stage.

Method. Accordingly we selected 11 diabetic patients, all of whom were well controlled on a diabetic regimen; that is, they were aglycosuric or nearly so, and clinically well. After a 15-hour fast, a specimen of blood was obtained from each patient and 100 grams of cotton seed oil was administered orally. Blood samples were taken at 3, 6 and 9 hours after the oil drink. Total lipoids were determined by the method of Ruckert.[19] This ingenious method is simple and accurate and has been checked against the more elaborate, time-consuming methods. Its principle is the same as the Gerber milk-fat method and it is free from the sources of error that were pointed out for the Stewart and White method. Emulsions of known quantities of fat as well as various dilutions of fat containing liquids are recovered with great accuracy.

Very briefly the technique for performing the test is as follows: A small quantity of serum (0.15 cc.) is drawn up into a specially constructed lipokrit pipette and mixed with a mixture of sulphuric acid (70 per cent, Sp. Gr. 1.616) which contains methylene blue, and amyl alcohol which contains anilin yellow. The proteins are hydrolyzed by the sulphuric acid and changed from colloidal state to a state of molecular dispersion. The fat is liberated and then dissolved by the amyl alcohol. The anilin yellow colors the dissolved fat a brilliant yellow which after centrifugalization collects above and is measured volumetrically on a graduated scale. The phosphatids dissolve in the alcoholic-sulphuric acid mixture and are re-precipitated as fatty acids. This fatty acid fraction rises gradually and in 24 hours it also is read off the graduated scale. The difference between the total fats and the neutral fat value equals the fatty acid fraction of the phosphatid, from which is readily computed the amount of phosphatid. For a detailed description of this method in English, see the article of Douglas Collins.[20] This investigator did not follow Ruckert's directions exactly as we did. He disregarded the immediate reading of neutral fat, and calculated his results for volume per cent instead of milligrams of total fat. The final step of computing the phosphatid value from its fatty acid fraction was omitted.

Results. The results of these fat absorption curves are recorded in Table 1, Columns 1A, 2A, 3A, 4A, 5A, 6A, 7A, 8A, 9A, 10A and 11A. With the exception of Cases 5 and 9 which continued to show a rise even at the 9th hour, the peak of absorption was reached at the 6th hour and by the 9th hour the lipoid values were approaching the fasting values. Ten days later these 11 patients were again given 100 grams of oil after fasting 15 hours. Blood specimens were taken just before the oil was drunk, 3, 6 and 9 hours after. At $2\frac{1}{2}$,

TABLE 1.—TOTAL BLOOD (SERUM) FATS OF 11 DIABETIC PATIENTS EXPRESSED IN MILLIGRAMS PER 100 CC. BEFORE 3, 6 AND 9 HOURS AFTER THE INGESTION OF 100 GRAMS OF COTTONSEED OIL (COLUMN A), AND (COLUMN B) 10 DAYS LATER WITH 1 MG. OF ADRENALIN (SUBCUTANEOUSLY).

Case No.	1		2		3		4		5		6		7		8		9		10		11	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Fasting	704	677	351	798	613	798	735	734	991	991	991	911	591	651	918	885	707	845	517	631	734	527
100 gm. oil per os: 2½ hrs. later . .	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.
3 hrs. later . .	863	818	607	766	871	918	951	862	1142	1197	998	966	774	798	1149	1046	951	925	778	886	838	663
5½ hrs. later . .	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	.. adr.	1 cc.	.. adr.	1 cc.	.. adr.	1 cc.	.. adr.	1 cc.
6 hrs. later . .	1579	758	775	965	1234	918	1111	1006	1150	1165	1030	882	846	743	1492	1181	1046	848	831	766	911	815
8½ hrs. later . .	..	..	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	1 cc. adr.	..	..	..	1 cc. adr.	..	1 cc. adr.
9 hrs. later . .	1196	..	656	878	1098	894	1041	870	1249	925	925	694	814	702	1430	1189	1085	..	531	758	831	814

5½ and 8½ hours after the ingestion of the oil 1 mg. (1 cc.) of adrenalin was given subcutaneously (total dosage 3 mg. in 6 hours). The effect of the adrenalin on the absorption curves was striking (see Table 1, Columns 1B, 2B, 3B, 4B, 5B, 6B, 7B, 8B, 9B, 10B and 11B). In all except one (Case 11), who was the only patient in the group taking a high-fat diet, the adrenalin caused a decided lowering of the blood lipoids as compared with the values for the lipoids when no adrenalin was given. This one exception (Case 11) was a young woman who had lost much weight, with suspected pulmonary tuberculosis, who in the adrenalin experiment became nauseated, developed tachycardia, experienced substernal pain, vertigo and was greatly distressed. Thus she should perhaps be excluded from this group, which consisted of healthy individuals on low-fat diets. Although all of the other patients experienced the physiologic effects of the adrenalin and commented on "a strange feeling, nervousness, dizziness, heart consciousness," none except Case 11 was distressed.

Discussion. It is reasonable to suppose that there is a hormonal influence on, if not regulation of, fat metabolism. So complex is fat metabolism that its exact mechanism has never been elucidated. The control of carbohydrate metabolism is better understood, and therefore the substances (adrenalin and insulin) which have been shown to influence carbohydrate utilization should be studied carefully in their effects on fat utilization. Oxidation of fat after a certain point requires simultaneous combustion of glucose. However, a hard and fast relationship of carbohydrate and fat content of the blood has never been demonstrated. It is known that carbohydrate is converted into fat and it is believed that fat may be converted into carbohydrate, but this mechanism is obscure. Indeed the form in which fat is absorbed is unknown. There has been much speculation concerning the rôle of hormones in fat metabolism. After studying the effects of pituitrin, adrenalin and other substances on fat metabolism, Raab[17] concluded that there was a regulated utilization of fat through adrenalin and insulin for the purpose of carbohydrate replacement maintaining the tissues with sugar. Cori, Cori and Buckwald[21] have stressed the important rôle played by the decreased utilization of blood sugar in epinephrin hyperglycemia. If a decrease in the utilization of blood sugar did occur after the injection of adrenalin in the patients observed, the lowering of the blood fats was probably due to the immediate utilization of the fat by the tissues. Had the experiment been continued over a longer period of time, there might have been a secondary rise of the blood fats with ketonemia, due to incomplete combustion of the fat. This suggests a possibility that the alternate use of adrenalin and insulin with high carbohydrate, high-fat diet might prove a valuable adjunct in convalescent and malnourished non-diabetic patients when optimum food utilization is desired.

Summary and Conclusions. 1. The administration of adrenalin in dosage sufficient to produce physiologic response causes a lowering of the increasing blood fats in the alimentary lipemia of diabetes mellitus.

2. This fact is significant as additional evidence supportive of the view that adrenalin has a direct regulatory effect on fat metabolism.

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REFERENCES.

1. Bock, A. V., Field, H., and Adair, G. S.: J. Metab. Res., 1923, **4**, 27.
2. Chauffard, A., Brodin, P., and Yovanovitch, R.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1924, **48**, 1573.
3. Labbé, M.: Ibid., p. 1581.
4. Campbell, W. R., and McLeod, J. J. R.: Medicine, 1924, **3**, 195.
5. Rabinowitch, I. M., and Mills, E. S.: J. Metab. Res., 1926, **7**, 87.
6. Christomanos, A. A.: Biochem. Ztschr., 1929, **214**, 482.
7. Rony, H. R., and Ching, T. T.: Proc. Soc. Exp. Biol. and Med., 1930, **27**, 533.
8. Stewart, C. P., and White, A. C.: Biochem. J., 1925, **19**, 840.
9. Himwich, H. E., and Spiers, M. A.: Am. J. Physiol., 1931, **97**, 649.
10. Himwich, H. E., and Fulton, J. F.: Ibid., p. 533.
11. Koskoff, V. D., and Dusser de Barenne, J. G.: Science, 1931, **74**, 550.
12. Long, C. H. N., and Venning, E. M.: Canadian Med. J., 1932, **26**, 461.
13. Long, C. H. N., and Venning, E. M.: J. Biol. Chem., 1932, **96**, 397.
14. Stoddard, J. L., and Drury, P. E.: Ibid., 1929, **84**, 741.
15. Page, I. H., and Pasternak, L.: Biochem. Ztschr., 1931, **232**, 295.
16. Fleish, A.: Ibid., 1926, **177**, 461.
17. Raab, W.: Ztschr. f. d. ges. Exp. Med., 1926, **49**, 179.
18. Bornstren, A., and Müller, E.: Biochem. Ztschr., 1921, **126**, 64.
19. Ruckert, W.: Klin. Wchnschr., 1931, **10**, 1853.
20. Collins, D. H.: Quart. J. Med., 1933, **2**, 267.
21. Cori, G T., Cori, C. F., and Buchwald, K. W.: J. Biol. Chem., 1930, **86**, 375.

THE DISTRIBUTION OF SUGAR AND CHLORID IN THE BLOOD OF DIABETIC INDIVIDUALS.

By Ennion S. Williams, M.D.,
RESIDENT IN CHEMISTRY, PENNSYLVANIA HOSPITAL,
AND
F. William Sunderman, M.D., Ph.D.,
ASSISTANT PROFESSOR OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

(From the Chemistry Department, Pennsylvania Hospital, and the Department of Research Medicine, University of Pennsylvania.)

The distribution in the corpuscles and the serum of the different components of whole blood has been studied by many investigators. Although the concentrations of the various constituents in the blood may be strikingly different in the corpuscles and in the serum, nevertheless, from freezing-point studies[1] it would appear that the cells

are in osmotic equilibrium with the serum. The sum of the osmotically active electrolytes in the corpuscles has been shown to equal the sum of the osmotically active electrolytes in the serum when calculated on a water basis, although the concentrations of the individual ions in the corpuscles and the serum are not equal. The non-electrolytes of small molecular size theoretically should be equally distributed and freely diffusible throughout both cells and serum. Concerning the various non-electrolytes there are data in the literature suggesting that glucose may not be freely diffusible and that its distribution between corpuscles and serum may be abnormal in pathologic conditions such as diabetes mellitus.

Chlorid has been regarded as one of the most mobile of the anions present in the blood, because of the readiness with which the concentration of chlorid can be reduced to make way for other anions. It has been suggested that changes in the concentration of BCl may serve as a regulator of the osmotic pressure for variations in the concentration of non-electrolytes. Herrick[2] has demonstrated an inverse relationship between chlorid and glucose in the whole blood. Ni[3] has found similar relationships in the blood of depancreatized dogs. Gram[4] believed that there was a reduction in chlorid concentration in the course of chronic nephritis which occurred as a compensation for the retention of non-protein nitrogenous substances. Sunderman, Austin and Williams[5] found an inverse relationship between glucose and chlorid concentration after the administration of insulin to diabetic patients, although freezing-point studies indicated that the reduction in glucose was not entirely compensated for osmotically by the increase in the chlorids.

Somogyi[6] reviewed the literature on the distribution of sugar in the blood in 1928. Certain earlier investigators had concluded from their analyses of cells washed in physiologic salt solution that corpuscles contained no fermentable sugar. Later investigators, by measuring the total reducing substances in the cells and serum, arrived at the view generally accepted until 1928 that there was a nearly equal distribution of blood sugar between the corpuscles and plasma, the ratio $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$ (concentration by volume) being on the average 1.1. Somogyi demonstrated that there was approximately 5 times as much non-fermentable reducing substance in the corpuscles as in the serum and that when the non-fermentable reducing substances were subtracted the ratio of sugar in the corpuscles to sugar in the serum was less than 1 (the average being 0.77) and was approximately the same for diabetic individuals as for non-diabetic individuals. John[7] found the ratio of $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$ (concentration by volume) to be lower for diabetic subjects than for non-diabetic subjects. His measurements apparently did not take into account the correction for non-fermentable reducing

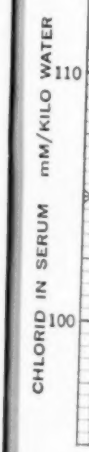
substances. On the other hand Folin and Svedberg[8] found the distribution ratio to be higher in diabetic than in non-diabetic individuals. They found a ratio $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$ (concentration by volume) of approximately 0.60 for non-diabetic and 0.69 for diabetic individuals. Bose[9] recently reported that the distribution ratio $\frac{\text{corpuscle sugar}}{\text{plasma sugar}}$ (concentration by volume) was lower in diabetic than in normal subjects. He considered the measurement of this ratio to be of prognostic value, the lower the distribution ratio the more severe the diabetes.

Foshay[10] found that the administration of insulin in diabetic patients altered the distribution of sugar in the corpuscles and in the plasma. He considered the finding of a low ratio an indication of approaching insulin shock. Trimble and Maddock[11] failed to confirm this finding. They found no change in the distribution ratio after insulin administration. Spannuth and Power[12] found the distribution ratio for glucose to be about the same in the diabetic and in the non-diabetic subject. After the administration of glucose they found the ratio to be unchanged in the normal person but to be decreased in the diabetic individual.

In consideration of these conflicting views, the present study, designed to measure the distribution of glucose and chlorid in the corpuscles and serum of normal individuals and of individuals suffering from diabetes mellitus, seemed desirable.

In all of the observations cited with respect to glucose the measurement of the glucose has been expressed in terms of volume of solution. Since in measurement of osmotic pressure results more concordant with theory are obtained if the concentration of solute is expressed in terms of the volume of solvent at its maximum density rather than in terms of volume of solution, the results of our measurements of glucose and chlorid have been calculated on a water basis. During the process of this investigation an article appeared by MacKay[13] in which when similar calculations were made, glucose was found to be freely diffusible and equally distributed in the water of the corpuscles and the plasma of heparinized blood. His data included the analysis of blood obtained from 2 diabetic patients.

Mosonyi[14] measured the partition of sugar in the blood following the ingestion of glucose and the administration of insulin respectively in dogs. Although his data did not include analyses of the water content of the corpuscles or serum, nevertheless, when reasonable approximations were made as to the water content of the corpuscles and serum, Mosonyi obtained results which in certain instances were incompatible with the observations of MacKay of an equal distribution of glucose in the water of the cells and the water of the serum. In fact Mosonyi found the concentrations of



glucose by volume to be higher in the cells than in the serum in 6 of his analyses.

Materials and Methods. Our studies were made on blood obtained from 5 normal individuals attached to the laboratory and from 22 patients suffering from diabetes mellitus attending the metabolic clinic of the Pennsylvania Hospital. After an overnight fast, venous blood was collected directly under oil without stasis. Samples were defibrinated and divided into two portions, both of which were centrifuged. The serum was removed from one portion and the other portion was stirred with a glass rod to insure an even remixture of the serum and the cells. Samples of the serum and whole defibrinated blood were analyzed for glucose within 20 minutes after

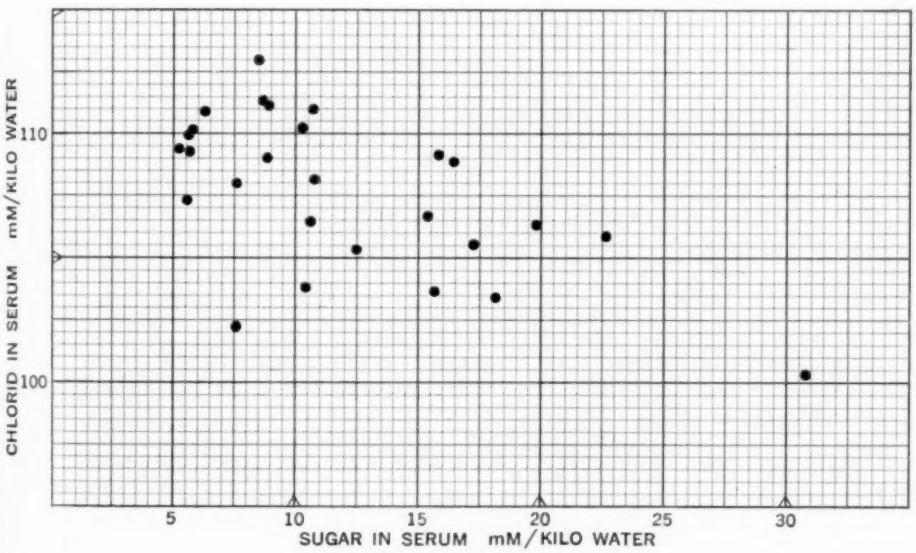


FIG. 1.—Sugar and chlorid in serum.

obtaining the specimens. The glucose measurements were made according to the Benedict method.[15] The other methods used in this study have been described in previous papers.

Calculations. For the calculation of the concentration of glucose and chlorid in the cells and the serum the following formulæ were used:

Symbols: X = concentration in grams of either glucose or chlorid
R = dry residue in grams
G = specific gravity
c, s, w. b. = cells, serum and whole blood respectively
% = percentage of cells or serum by volume

( ) = concentration in grams per liter of serum or cells
[ ] = concentration in grams per kilogram of water
{ } = concentration in grams per kilogram of serum or cells

The concentration of sugar or chlorid per kilogram of water in serum:

$$(1) \quad [X]_s = \frac{(X)_s \times 1000}{G_s \ (1000 - \{R\}_s)}$$

The concentration of sugar or chlorid per kilogram of water in cells:

$$(2) \quad [X]_c = \frac{(X)_c \times 1000}{G_c \ (1000 - \{R\}_c)}$$

where

$$(2a) \quad (X)_c = \frac{100 \ (X)_{w.\,b.} - \% \ s \ (X)_s}{\% \ c}$$

$$(2b) \quad G_c = \frac{100 \ G_{w.\,b.} - \% \ s \ G_s}{\% \ c}$$

$$(2c) \quad (R)_c = \frac{100 \ \{R\}_{w.\,b.} \times G_{w.\,b.} - \% \ s \ \{R\} \ G_s}{\% \ c}$$

$$(2d) \quad \{R\}_c = \frac{(R)_c}{G_c}$$

Results. The results of the analysis of the bloods of 22 diabetic patients and 5 normal subjects are presented in Table 1. When the concentrations of glucose were calculated on a water basis the average ratio $\frac{\text{corpuscle sugar}}{\text{serum sugar}}$ was found to be 1.023 ± 0.0088 (S. E.) for the diabetic patients and 1.035 ± 0.025 (S. E.) for the normal individuals.

The ratio of $\frac{\text{corpuscle chlorid}}{\text{serum chlorid}}$ was found to average 0.683 ± 0.004 (S. E.) for the diabetic bloods and 0.672 ± 0.017 (S. E.) for the normal bloods. When the ratio found in the diabetic blood was corrected to 100-per cent oxygenation, the corrected ratio was 0.66.* The pH of the serum and of the whole blood was measured by means of the glass electrode in 9 of the specimens obtained from diabetic patients. Since all of the measurements fell within relatively narrow limits (0.13 of pH), the average pH (7.464) of the 9 measurements was used as the average of the entire series. The degree of oxygena-

* The correction was made by the formula

$$C = 0.1 \ (pHs - 6.6) \ \frac{\text{reduced Hb}}{\text{total Hb}}$$

where c is the amount by which the observed ratios must be decreased to give the ratio for completely oxygenated blood (16).

TABLE 1.—RESULTS OF ANALYSES. DIABETIC INDIVIDUALS.

TABLE 1.—RESULTS OF ANALYSES. DIABETIC INDIVIDUALS.

Case.	Sugar		Chlorid		Cell volume.	Sp. Gr.		Solids		Ratio Corp. sugar / Serum sugar.	Ratio Corp. Cl. / Serum Cl.
	Corp.	Serum.	Corp.	Serum.		Corp.	Serum.	Corp.	Serum.		
	mM/Kg of water.	mM/Kg of water.	mM/Kg of water.	mM/Kg of water.	Per cent.	20°/20°	20°/20°	Gm/Kg of corp.	Gm/Kg of serum.	Water basis	Water basis.
40377	10.25	10.71	73.4	108.1	42.2	1.0924	1.0286	329.09	92.77	0.96	0.68
65859	7.85	7.57	71.2	102.3	47.8	1.0944	1.0296	337.26	93.50	1.04	0.70
1765	15.44	15.64	69.5	103.6	44.0	1.0939	1.0280	328.54	87.72	0.99	0.67
18761	9.99	10.67	70.2	106.5	43.3	1.0915	1.0272	318.84	86.99	0.93	0.66
252	8.38	8.52	77.0	112.9	41.0	1.0839	1.0260	298.58	78.96	0.98	0.68
61563	12.13	11.76	73.9	110.9	39.4	1.0909	1.0290	320.88	93.9	1.03	0.67
27131	18.38	18.13	72.1	103.4	43.0	1.0851	1.0276	292.35	85.08	1.01	0.70
61973	12.70	12.48	73.3	105.4	45.2	1.0956	1.0273	338.50	85.78	1.02	0.70
49214 B	10.09	10.36	69.1	110.2	39.3	1.0980	1.0271	327.15	87.37	0.98	0.63
26900 U. H.	9.67	8.88	76.5	109.0	42.4	1.0958	1.0281	358.57	90.11	1.09	0.70
26264	18.25	17.31	72.1	105.5	42.6	1.0979	1.0266	330.04	85.36	1.05	0.68
2974 B	9.30	8.91	84.3	111.1	40.6	1.1062	1.0261	376.13	81.27	1.04	0.76
279	23.11	22.71	69.0	105.8	46.0	1.0926	1.0278	324.24	88.53	1.02	0.65
82062	16.22	15.32	68.7	106.7	48.2	1.0893	1.0287	323.57	90.25	1.06	0.64
37969	8.13	7.60	74.8	107.9	44.8	1.0953	1.0263	337.93	82.61	1.07	0.69
62155	6.71	6.43	72.9	110.8	43.3	1.0988	1.0308	354.32	95.54	1.04	0.66
2771 A	16.46	16.33	86.1	108.8	49.0	1.0922	1.0301	316.6	94.9	1.01	0.79
2041 A	15.89	15.94	74.5	108.6	50.1	1.0912	1.0249	322.64	78.48	1.00	0.69
39579	9.39	8.72	78.5	111.4	44.6	1.0980	1.0301	334.1	96.87	1.08	0.71
15777	10.92	10.49	60.6	103.8	37.5	1.0968	1.0282	318.8	88.40	1.04	0.58
2041 A	20.64	19.61	71.1	106.4	51.2	1.0930	1.0275	330.6	86.45	1.05	0.67
4353 B	31.24	30.79	72.4	100.4	43.2	1.0940	1.0281	339.67	86.48	1.02	0.72
NORMAL INDIVIDUALS.											
100	5.55	5.72	72.0	109.6	46.3	1.0981	1.0265	349.75	84.25	0.97	0.66
101	5.74	5.79	67.5	110.0	45.0	1.0958	1.0263	345.5	83.2	0.99	0.61
102	6.30	5.74	74.8	107.3	46.3	1.0961	1.0283	379.3	81.3	1.10	0.70
103	5.95	5.76	75.6	109.2	52.0	1.0955	1.0280	372.2	89.6	1.03	0.69
104	6.35	5.89	76.5	109.1	50.0	1.0924	1.0279	333.76	91.7	1.08	0.70

tion of the venous blood was assumed to be approximately 75 per cent saturated. Any moderate variation from this figure would not change this correction to any significant degree.

While there appeared to be no definite linear relationship between the level of glucose and the level of chlorid from subject to subject in either whole blood, corpuscles, or serum, calculated on either a liter or a water basis, nevertheless, in general there was a tendency for the high values of sugar to be associated with the low values of chlorid and *vice versa*. In Fig. 1 we have plotted the values for glucose and chlorid of the serum on a water basis, demonstrating the scattering observed.

Discussion. Peters and van Slyke[18] have pointed out that it was doubtful at the time of their publication whether the distribution of chlorid between cells and serum could be explained purely on the basis of the Donnan theory because of the deviation of analytical data from the calculated values. The factor for the chlorid ratio is about 0.8 to 0.9 times that for the bicarbonate. The presence of an organic chlorid which might account for this discrepancy has never been demonstrated in blood. From recent experiments demonstrating the occlusion of chlorid by fat[19] we suggest the possibility that a fraction of chlorid in the cells might be held by the lipoids and as such be incapable of diffusion.

When corrected for changes in the CO_2 and oxygen tension, the ratio $\frac{\text{corpuscle chlorid}}{\text{serum chlorid}}$ does not appear to deviate in a series of pathologic states studied from the normal, as shown in the following table:

	pH.	$\frac{\text{Clc}}{\text{r Cls}}$
Hastings *et al.*		
Normal	7.38	0.689
Nephritis	7.35	0.700
Pneumonia	7.42	0.674
	pH.	$\frac{\text{Clc}}{\text{r Cls}}$
Muntwyler *et al.*		
Various conditions	7.42	0.669
Williams and Sunderman		
Diabetics	7.46	0.660

When calculated on a water basis, sugar in the blood appears to be freely diffusible between the corpuscles and serum in the blood of normal subjects and of patients suffering from diabetes mellitus. Benedict reported that his method for the measurement of glucose included about 3 to 5 mg. per cent of non-fermentable reducing substances. Since it is generally believed that the cells contain the greater part of these substances this difference may account for the fact that our ratio of $\frac{\text{corpuscle sugar}}{\text{serum sugar}}$ is slightly above unity.

Conclusions. The distribution of glucose and chlorid between the corpuscles and the serum has been studied in the blood obtained from diabetic patients and normal patients. In both the diabetic and normal blood the glucose was found to be approximately equally distributed throughout the water of the corpuscles and the serum. This is in agreement with the findings of MacKay.

The distribution of the chlorid in the water of the cells and the water of the serum of diabetic blood did not differ essentially from the distribution found by other investigators in normal and pathologic blood.

No consistent relationship between the level of glucose and the level of chlorid in the whole blood, corpuscles, or serum was observed.

BIBLIOGRAPHY.

1. Collins, D. A., and Scott, F. H.: J. Biol. Chem., 1932, **97**, 189.
2. Herrick, W. W.: J. Lab. and Clin. Med., 1924, **9**, 458.
3. Ni, T. G.: Am. J. Physiol., 1926, **77**, 158.
4. Gram, H. C.: J. Biol. Chem., 1923, **56**, 593.
5. Sunderman, F. W., Austin, J. H., and Williams, P.: J. Clin. Invest., 1932, **11**, 1261.
6. Somogyi, M.: J. Biol. Chem., 1928, **78**, 117.
7. John, H. J.: J. Lab. and Clin. Med., 1930, **15**, 713.
8. Folin, O. and Svedberg, A.: J. Biol. Chem., 1930, **88**, 715.
9. Bose, J. P.: Indian Med. Gaz., 1932, **67**, 541.
10. Foshay, L.: Arch. Int. Med., 1927, **40**, 666.
11. Trimble, H. C., and Maddock, S. J.: J. Biol. Chem., 1928, **78**, 323.
12. Spannuth, J. R., and Power, M. H.: Ibid., 1931, **93**, 343.
13. MacKay, E. M.: Ibid., 1932, **97**, 685.
14. Mosonyi, L.: Biochem. Ztschr., 1932, **256**, 308.
15. Benedict, S. R.: J. Biol. Chem., 1931, **92**, 141.
16. Hastings, A. B., Sendroy, J., Jr., McIntosh, J. F., and Van Slyke, D. D.: Ibid., 1928, **79**, 193.
17. Muntwyler, E., Myers, V. C., and Way, C. T.: Ibid., 1931, **92**, 721.
18. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. I. Interpretations, The Williams and Wilkins Company, Baltimore, 1931.
19. Sunderman, F. W., and Williams, P.: J. Biol. Chem., 1931, **92**, 99.

STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

I. Observations on the Alterations in the Rhythm of the Heart Preceding Syncopal Seizures in a Patient with Normal Sinus Rhythm.

By Sidney P. Schwartz, M.D.,
CARDIOGRAPHER AND ASSOCIATE ATTENDING PHYSICIAN,
AND
Abraham Jezer, M.D.,
ASSISTANT IN MEDICINE IN THE MONTEFIORE HOSPITAL,
NEW YORK CITY.

(From the Medical Division of the Montefiore Hospital, Service of Dr. Leopold Lichtwitz.)

There are exceedingly few observations on the disturbances in the rhythm of the heart which precede the onset of spontaneously

developed transient ventricular fibrillation in man. A careful examination of the electrocardiograms of the few instances of ventricular fibrillation reported in the literature since the introduction of the electrocardiograph reveals a meager knowledge of this mechanism; yet, experiences at the Montefiore Hospital within the past few years with such patients lead to the belief that ventricular fibrillation as a cause of recurrent syncopal attacks is, in all probability, much more commonly the cause of Stokes-Adams seizures than has been suspected hitherto.[1,2,3]

It is the purpose of this and similar studies that follow it, to describe the natural course of syncopal attacks due to ventricular fibrillation as they occur in man, and to point out how this mechanism is ushered in, and in what respects these pre-fibrillatory periods are totally different from any other type of ventricular irregularity encountered in practice. Only certain features of these pre-fibrillatory irregularities are pathognomonic for ventricular fibrillation.

The sequential disturbances of normal sinus rhythm preceding syncopal attacks are delineated in the following observations:

Case Report. — E. M., a boy, aged 17, was transferred to Montefiore Hospital from the Neurological Institute on December 20, 1932, and died on January 18, 1933.

He was perfectly well until 2 years before his admission to the hospital, when he contracted a "severe head cold" which subsided under local treatment. In November, 1932, he complained again of a "severe head cold" which was accompanied within 2 days by fever, occasional cough and diarrhea. On the morning of November 21, 1932, he noticed that his toes felt numb. On the same afternoon he found that his legs were weak and he was unable to void or move his bowels. On the following day the power in his legs became progressively weaker. Four days after the onset of his illness, he had lost all power in his legs and he observed a distinct difference in the temperature of his bath when he compared sensations between the upper and lower extremities. At this time he had to be catheterized because he was unable to void and from then on his bladder was irrigated once a day.

Physical examination on admission to Montefiore Hospital revealed an undernourished, brown-skinned youth who was comparatively free from distress. He was lying flat in bed. His respirations were 22 per minute. His heart rate averaged 92 beats per minute and the rhythm was regular. His temperature ranged between 98° and 101° F. There were 2 large echymotic areas over his sacrum and heels and there were several decubitus ulcers on his back. His eye grounds revealed temporal pallor in both disks. The apical impulse of the heart was in the 5th intercostal space within the midclavicular line. The heart sounds were of good quality. There were no murmurs. The lung fields were clear. The liver and spleen were not palpable. The legs showed no edema. There was a flaccid paraplegia with practically all reflexes absent except the right knee jerk, which was very feeble. A definite sensory level could be demonstrated in the region of the 7th dorsal vertebra.

The Wassermann reaction of the blood and spinal fluid was negative and the cerebrospinal fluid was clear, colorless, and not under pressure. The urine showed a considerable number of pus cells and there was moderate secondary anemia.

Course During Stay in Hospital. During his stay in the hospital, the boy's fever persisted. He was first seen during a seizure of unconsciousness

on the morning of January 16, 1933. His breathing was stertorous and difficult, his head and eyes were turned to one side, and there were mild tonic convulsions of his upper extremities. Two or 3 minutes after this episode the breathing returned to normal but he could not respond when addressed. He attempted to turn on his right side, closed his eyes and again had a mild "attack" of loss of consciousness, with stertorous breathing, extension of his head backward and to the side and deviation of his eyes to the right. Atonic contractions of his upper limbs were noted to follow, and during this episode the heart sounds were inaudible and his pulses were not palpable.

The eye grounds as observed by Dr. M. M. Abeles were unusually interesting at this time. During the collapse of the circulation when the heart sounds were inaudible and the blood pressure could not be recorded, the blood stream in the retinal vessels appeared fragmented. Some of the retinal veins had lost their contour completely and could be recognized only when "spurts" of blood corpuscles would flow through them when the heart beat again. As soon as the boy's pulse became palpable following an effectual ventricular contraction, all of the retinal vessels could be outlined.

Because of the increasing frequency of these recurrent periods of unconsciousness and on the assumption that these episodes were due to arrest of the circulation as a result of stoppage of the ventricles, an attempt was made to inject 0.5 cc. of a 1:1000 solution of adrenalin directly into the heart during a long seizure of unconsciousness. Immediately after the injection the boy became extremely restless. An occasional pulse beat came through at the wrist but there was a sudden tonic closure of the lower jaw and there were innumerable clonic convulsions of all of his limbs with marked frothing at the mouth and very forced difficult breathing, finally ending in apnea and Cheyne-Stokes respirations with the boy losing total consciousness and becoming comatose.

For the next 5 hours he was in a state resembling "status epilepticus." The pupils were widely dilated and fixed to light. The eye movements were in a vertical plane only. There was bilateral ankle clonus. There were tonic contractions of the muscles of the body with rigidity simulating "decerebrate" rigidity. In addition there were innumerable convulsions.

The heart rhythm during this time was reported as being totally irregular with a pulse deficit, resembling the rhythm of auricular fibrillation with a very rapid ventricular rate.

On the following morning, January 17, 1933, the patient was still confused and dull although he no longer exhibited convulsive movements. At 1.00 P.M. of that day his pulse and heart rhythm were regular and averaged 110 beats per minute. When seen by us he spoke more clearly, and later as he was watched during the day his heart rate was noted to be rapid and irregular again and interrupted by a bigeminy. This arrhythmia alternated with long periods of regular rhythm and a ventricular rate of 110 beats per minute.

A hyperresonant note over the left half of his chest with displacement of his heart to the right was noted for the first time on this day. This was diagnosed and confirmed by radiograms to be due to air in the left pleural cavity following the attempt to inject adrenalin in the heart cavities on the previous day, when the absence of the boy's pulse was attributed to "ventricular standstill."

On January 18, 1933, the boy suffered from complete amnesia for several hours and still continued to have recurrent seizures of unconsciousness. On the morning of that day, however, the cerebral accidents were considered for the first time to be of cardiac origin and repeated electrocardiograms taken over long periods and correlated with his clinical manifestations during syncopal seizures revealed these attacks to be due to transient ventricular fibrillation.

He died in a long seizure of ventricular fibrillation which started with loss of consciousness and stertorous breathing and ended in apnea with a total collapse of the circulation.

The Cardiac Mechanism. The usual average ventricular rate prior to the onset of syncopal seizures was 92 beats per minute and the rhythm was regular. It was not influenced by deep respiratory effort and pressure over either carotid artery did not slow it. During the time that syncopal seizures were recurring frequently, the basic ventricular rate averaged 150 beats per minute independent of the presence of any premature ventricular beats (Fig. *A*, 1*A–B*). The main ventricular deflections were supraventricular in form and the *P* wave preceding each was superimposed upon the *T* wave.

For long periods of from several minutes to several hours at a time, the rapid regular basic sinus rhythm would alternate with a bigeminal rhythm. At first this rhythm was occasionally interrupted by premature beats of the ventricles which appeared after every 3d "basic" ventricular complex (Fig. *A*, 1*B–C*). These premature beats were opposite in direction to the main ventricular deflections and they were audible at the apical region of the heart and palpable at the wrist.

Soon the bigeminal rhythm would be interrupted by what appeared clinically as irregular "pulse pauses" of from 35 seconds to 1½ minutes in duration (Fig. *A*, 2*B*, 3*A–B–C–D;* Fig. *B*, 1*A*).

As these "pulse pauses" were studied with the patient in the electrocardiographic circuit and the heart sounds and pulses were compared with the movements of the galvanometer string, it was observed that they were the result of rapid ventricular oscillations, only the first 2 or 3 of which could be felt at the wrist or heard at the apical region of the heart. If these rapid and recurring ventricular oscillations lasted at least 8 seconds, then the patient shut his eyes momentarily and marked pallor of the face ensued. If the duration of these ventricular oscillations was 20 seconds, but not more than 40 seconds in duration, a typical Stokes-Adams syndrome would follow with loss of consciousness, stertorous breathing, convulsive movements of the body, and incontinence of feces and urine. Spontaneous revival would take place with the first effectual contraction of the ventricles as could be seen from watching the galvanometer string.

The basic ventricular complexes following each alternate premature ventricular beat during the presence of regular bigeminal rhythm were preceded by a distinct *P* wave with a *P–R* interval measuring 0.12 seconds (Fig. *A*, 2*A–B*). The addition of any further extra ventricular deflections to this existing bigeminal rhythm completely disrupted this sequence of events so as to produce an irregular and rapid ventricular rate with a pulse deficit simulating very closely the rhythm of auricular fibrillation. At such times the auricular complexes could hardly be discerned in the electrocardiograms

except occasionally, when they would reappear with the reëstablishment of the bigeminal rhythm (Fig. *A*, 2, 3*B–C*).

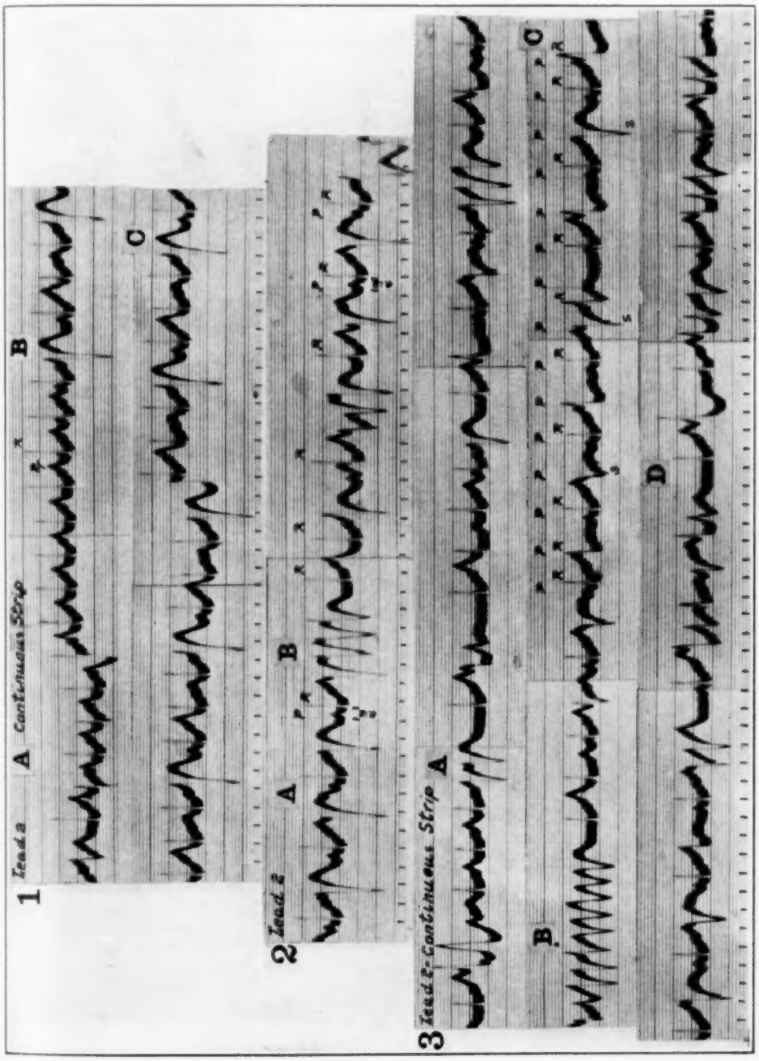


FIG. *A.—1A–B*, The basic ventricular rate is accelerated to 150 beats per minute. The main ventricular complex is upright and the *T* wave is superimposed upon the *P* wave. *B–C*, A premature ventricular beat appears after every third ventricular complex. It is opposite in direction to the main ventricular deflection. *2A*, The basic rhythm is interrupted by alternate premature ventricular beats. *B*, Recurrent ventricular oscillations, the intial beat of which is similar to the alternate premature ventricular beats. Note the irregular ventricular rate due to the haphazard appearance of multiple premature ventricular beats. *3B*, Recurrent ventricular oscillations, only the first two or three of which could be felt at the pulse or heard at the apical region of the heart, resulting in "pulse pauses." *B–C*, The auricular rate is not disturbed during the presence of alternate premature ventricular beats.

Each of the "pulse pauses" consists electrocardiographically of groups of three or more recurrent ventricular oscillations so superimposed upon each other as to increase their rate to almost 300 per minute. They are characterized by ventricular deflections of variable size in height, each group being ushered in by an "initial"

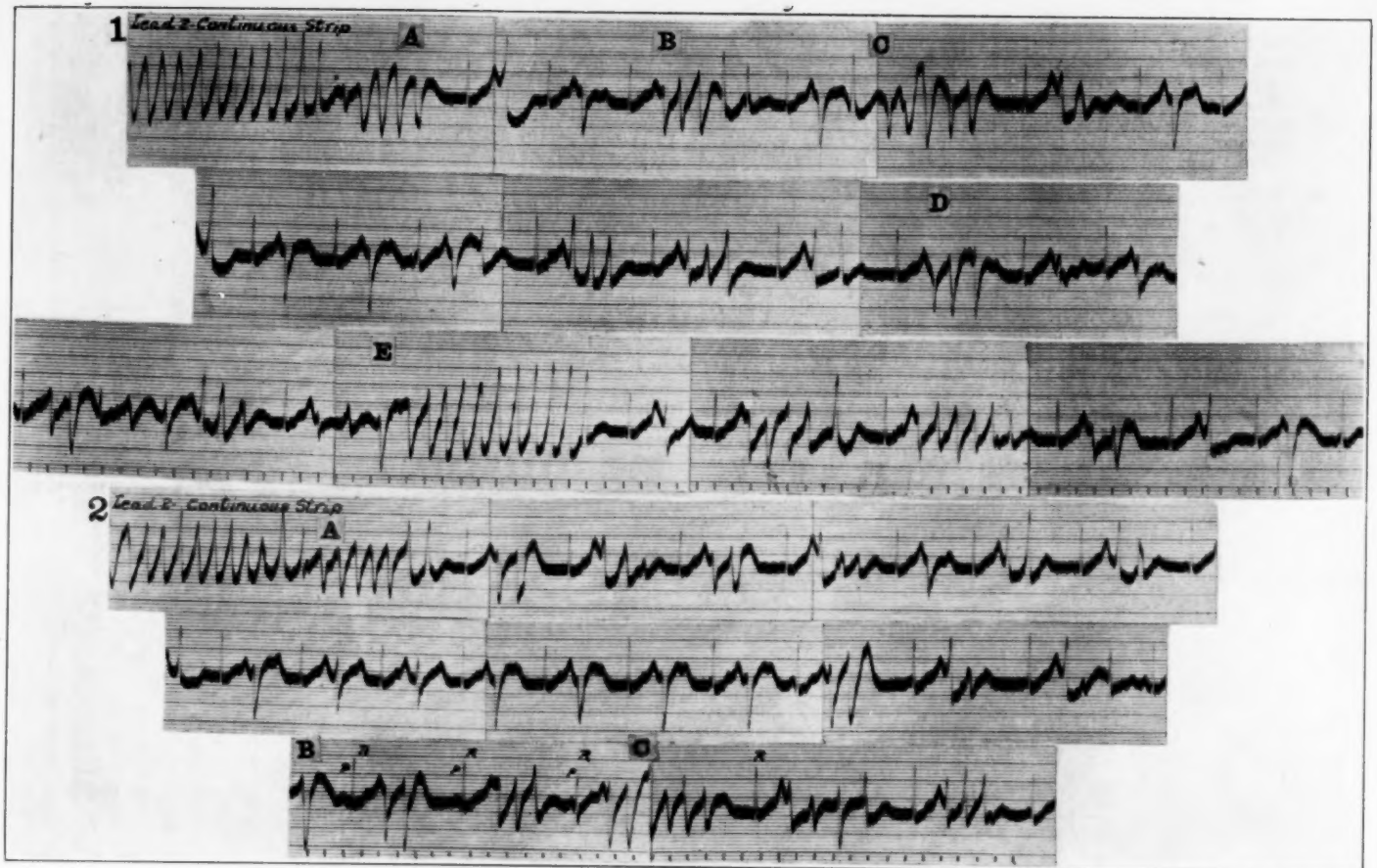


FIG. B.—1A–B–C–D–E, The recurrent ventricular oscillations are variable in size, shape and form. There is no distinct base line and they change abruptly both in voltage and direction from time to time. Each group of recurrent ventricular oscillations may be ended by a postundulatory pause (*A* and *E*) or by recurrent extrasystoles (*B*). 2*B–C*. Note the auricular complex preceding the basic ventricular complex is variable in shape, size and form depending upon its nearness to the ventricular complex.

ventricular complex which is most often opposite in direction to the main ventricular deflection of the basic rhythm. This "initial" beat preceding each short recurrent group of ventricular oscillations is usually at a definite and equal distance from the preceding basic beat. It follows an upwardly directed *P* wave or occurs simultaneously with it. It is very likely, however, that the presence of this "initial" beat bears no relationship to the preceding auricular complex and that it is an independent extra ventricular contraction which arises spontaneously from the ventricles and is fortuitously placed at this interval from the *P* wave. For if this "initial" beat were the result of an impulse arising in the auricle, it should be of the same shape, size, and form and be always at a certain distance from the *P* wave preceding it. But it has been pointed out that this is not so since some of the "initial" beats are occasionally opposite in direction to the usual forms present, and yet the *P* wave preceding these is at the same interval apart.

The ventricular oscillations which follow this "initial" ventricular beat increase in size from beat to beat. They present no distinct isoelectric line and after several of these beats have occurred, they may change abruptly in direction and in shape, size, and form, being more widely spaced as the mechanism is ended by a postundulatory pause.

Each of these recurrent short runs of ventricular oscillations ends with a postundulatory pause and is followed immediately by a basic ventricular complex which may or may not be preceded by a definite *P* wave with a well-defined *P–R* interval (Fig. *B*, 2*B–C*).

The basic ventricular complexes remain of the same shape and size, whether they follow a *P* wave at a definite *P–R* interval or whether they follow a postundulatory pause, and are not preceded by an auricular beat, indicating that the latter ventricular beats originate probably in the upper part of the auriculoventricular node and are independent of the auricular excitatory process originating in the normal sinus pacemaker.

Discussion. These electrocardiograms show that the preliminary disturbances which disrupted the normal cardiac mechanism in this boy prior to the onset of syncopal seizures due to ventricular fibrillation are of a very distinct nature.

They represent essentially a normal sinus rhythm with a rapid rate which is at first interrupted by the occasional interposition of premature ventricular beats of a definite shape or form. These increase in frequency so as to appear alternately at first. There are then added to these premature ventricular beats, in an irregular and unpredictable manner, groups of two or more recurrent and superimposed aberrant ventricular oscillations which, because of their frustrate character, produce "pulse pauses" with corresponding absent heart sounds.

The "pulse pauses" alternate in a haphazard fashion with an

abruptly both in voltage and direction from time to time. Each group of recurrent ventricular oscillations may be ended by a postundulatory pause (*A* and *E*) or by recurrent extrasystoles (*B*). 2*B*–*C* Note the auricular complex preceding the basic ventricular complex is variable in shape, size and

irregular ventricular rate, due partly to impulses originating in the auriculoventricular node and partly to recurrent extraventricular contractions that are frequently followed by normal ventricular complexes. These latter are preceded at regular intervals by an auricular contraction, which apparently arises from the sinus node.

There is thus a definite interplay of two centers within the heart, each sending out impulses at its own rate, the sinus node gaining the ascendency when a definite *P* wave is seen preceding the basic ventricular complex at an interval of 0.12 second and the auriculoventricular node becoming the pacemaker after the short postundulatory pauses that follow the interruption of normal rhythm by at least two or more recurrent ventricular oscillations.

These recurrent groups of ventricular oscillations are short runs of ventricular fibrillation. It is their interposition in the electrocardiographic tracings which indicate that any Stokes-Adams seizures that may have developed or will develop in any one patient subsequent to their appearance are due to the persistence or to the perpetuation of their mechanism.

It may be argued and justly so, that since these accompanying records were obtained only a short time prior to death, they represent terminal cardiac irregularities such as have been described by Gallavardin and his associates[4,5] and considered by them as characteristically "pre-fibrillatory" in nature.

These observers have classified as pre-fibrillatory arrhythmias a type of irregularity of the ventricles consisting of salvos of polymorphous extrasystoles, each of which is distinctly separated from the other, some with and others without any compensatory pauses and usually observed only terminally before death. Levy[6] has termed these alterations in rhythm "ventricular anarchy" because of the complex, irregularly alternating and bizarre nature of the ventricular deflections which make up these arrhythmias and which appear shortly before the death of those in whom they are seen.

Such alterations in rhythm have also been observed in the course of auricular fibrillation following overdosage with digitalis bodies.[7] Others have been noted as being more regular in sequence and alternating in character.[8] Still another mechanism consists of shorter and longer runs of a regular ventricular tachycardia with interpolation of polymorphous extrasystoles occasionally interrupting the basically accelerated heart.[9] Finally, even the generally accepted runs of ectopic supraventricular tachycardias, the so-called Maladie de Bouveret of the French, have been considered as being the premonitory mechanism of ventricular fibrillation, since such tachycardias have been seen to precede sudden death in many patients in whom they have appeared abruptly.

The criticism of the assumption that any irregular rapid and bizarre action of the heart or regular ectopic ventricular tachycardia is necessarily a "pre-fibrillatory" state of the ventricles is that there

are few records available of the end periods of these alterations in rhythm to prove that ventricular fibrillation has been the terminal phenomenon.

On the contrary, it would appear from recent studies at the Montefiore Hospital that patients dying in the course of a tachycardia of ventricular origin may go into ventricular standstill without any evidence of ventricular fibrillation. Indeed, judging from other evidences obtained of the dying heart,[10] it would appear that ventricular standstill is the rule rather than the exception in the "ultimum moriens" of the heart. Again when short runs of ventricular fibrillation have been observed as terminal phenomena they have been preceded and followed by irregular standstill of the ventricles with a marked slowing of the heart and not an acceleration as was present in this boy.[11]

Furthermore, these short runs of ventricular fibrillation described in this study, which may be appreciated from their pictorial representation much better than from the verbal descriptions, resemble in every respect similar graphic events observed to precede syncopal accidents in other patients in whom electrocardiograms obtained during major syncopal attacks revealed the underlying mechanism to be due to transient ventricular fibrillation. Some of these patients are still living 3 years after the onset of their seizures.

Summary and Conclusions. 1. Clinical manifestations were correlated with electrocardiograms of the alterations in the rhythm of the heart of a boy with infectious myelitis during a period when he was experiencing recurrent syncopal attacks, each of several minutes duration.

2. Prior to such seizures there was at first an acceleration of the basic sinus rate from an average of 90 to 150 beats per minute, but the rhythm was regular.

3. Sooner or later, in an unpredictable manner, premature ventricular beats began to disrupt the basic rhythm, first appearing after every fourth normal beat and then alternately after every other normal beat.

4. To these premature beats there were added from time to time recurrent groups of aberrant ventricular oscillations, only the first 2 or 3 of which could be heard at the apical region of the heart or felt at the pulse, thus resulting in periodic irregular "pulse pauses."

5. When the duration of these "pulse pauses" was only 8 or 10 seconds, there was momentary loss of consciousness with pallor of the skin. If they lasted between 20 and 40 seconds there was loss of consciousness. If they were of a duration longer than 40 seconds, there resulted a typical Stokes-Adams seizure with loss of consciousness, epileptiform convulsions, incontinence of feces and urine and stertorous breathing ending in apnea with intense cyanosis.

6. These recurrent periods of aberrant ventricular oscillations are short runs of ventricular fibrillation and their presence in the

electrocardiographic tracings was the most characteristic feature of the alterations in the rhythm of the heart that preceded syncopal seizures in this patient.

REFERENCES.

1. Schwartz, S. P.: Arch. Int. Med., 1932, **49**, 282.
2. Schwartz, S. P., and Jezer, A.: Ibid., 1932, **50**, 450.
3. Schwartz, S. P., and Jezer, A.: Med. Clin. North America, 1933, **17**, 213.
4. Gallavardin, L.: Arch. des mal. du coeur, 1921, **14**, 481.
5. Froment, R.: Les tachycardies paroxystiques ventriculaires, Paris, Masson & Cie, 1932.
6. Levy, J. R.: Les anomalies du complexe ventriculaire electrique. Leur Importance en Clinique, Paris, Masson & Cie, 1929.
7. Gallavardin, L.: J. de méd. de Lyon, 1926, **7**, 449.
8. Gallamaerts, E.: Étude electrocardiographique de la tachycardie paroxystique, Thèse de Bruxelles, 1924.
9. Gallavardin, L., and Veil, P.: Arch. des mal. du coeur, 1929, **22**, 25.
10. Turner, B. K.: Am. Heart J., 1930–1931, **6**, 743.
11. Dieuaide, F. R., and Davidson, E. C.: Arch. Int. Med., 1921, **28**, 663.

STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

II. Observations on the Alterations in the Rhythm of the Heart Preceding Syncopal Seizures in a Woman with Transient Auriculoventricular Dissociation.

By Sidney P. Schwartz, M.D.,
CARDIOGRAPHER AND ASSOCIATE ATTENDING PHYSICIAN, MONTEFIORE HOSPITAL
AND
Louis Hauswirth, M.D.,
DIRECTOR OF THE MEDICAL DIVISION, SYDENHAM HOSPITAL, NEW YORK CITY.

(From the Medical Division of the Montefiore Hospital, Service of Dr. Leopold Lichtwitz and the Medical Division of the Sydenham Hospital.)

From previous observations on the alterations in the rhythm of the heart which precede ventricular fibrillation,[1] it was to be expected that not every patient subject to transient seizures of ventricular fibrillation would have this abnormal mechanism ushered in, in exactly the same manner. Nevertheless, while fundamentally the basic rhythm may be different in individuals subject to such seizures, preliminary disturbances heralding transient periods of ventricular fibrillation associated with syncope are somewhat similar.

The following case demonstrates the clinical and graphic manifestations preceding transient ventricular fibrillation in a woman who ordinarily showed partial heart block alternating with normal sinus rhythm.

Case Report.—E. E., a female, aged 56 years, was first seen by one of us (L. H.) during the second week of April, 1932. She complained of recurrent attacks of unconsciousness accompanied at times by convulsions, of head-

aches and shortness of breath on climbing stairs. These symptoms were of three months' duration.

In January, 1932, she first began to experience what she described as "short fainting spells." Suddenly and without any warning signs, her usual routine would be interrupted by a feeling of "light headedness," at first lasting only a few seconds at a time but then increasing in duration as the symptoms progressed. Things would get black before her eyes and there were alternating periods of light and darkness lasting as long as a half hour, during which she felt faint, nauseated, and was compelled to sit in one place. Such episodes would come and go in brief paroxysms and on one occasion she fell to the floor, unconscious of her surroundings and had to be helped to bed. Peculiarly enough, when seen by a physician on a day following a prolonged seizure of syncope, her heart rate was 70 beats per minute and the rhythm was noted to be regular. The longer attacks of unconsciousness became more frequent during the month of February, 1932. At first she would have them for a few hours each day and then she would be free from such seizures for several days at a time. Now, these attacks were often accompanied by incontinence of urine and of feces, in addition to what the family described as "convulsions." These seizures must have taken place during her sleep also, for she would be frequently awakened to find her bed linen soiled, although she could not remember anything that took place previously. In between such attacks she would feel perfectly well and be up and about as if nothing had happened to her. During the ensuing 2 months she began to complain of persistent pains in the right upper quadrant in addition to her other symptoms, and in April, 1932, she developed an elevation of temperature accompanied by nausea and vomiting. Because of these complications she was admitted to the private pavilion of Sydenham Hospital for study and observation.

Physical examination at that time revealed a well-preserved woman, alert and intelligent, who answered questions rationally. Her right carotid artery was slightly thickened and tortuous. The apical impulse of her heart was in the 6th intercostal space in the anterior axillary line. The heart sounds were of good quality and the first sound was partly replaced by a loud blowing systolic murmur. The aortic second sound was slightly accentuated. The heart rate averaged 75 beats per minute and the rhythm was regular. The blood pressure was 229 systolic and 120 diastolic. A few moist râles could be heard over the bases of the lungs posteriorly. The abdomen showed slight rigidity in the right upper quadrant. The edge of the liver was not felt. There was a round mass about the size of a small orange palpable about 4 cm. below the right costal margin in the mid-clavicular line. It was extremely tender. The lower extremities showed no edema.

Because of the persistent signs in the abdomen, the patient was operated upon for cholecystitis during the third week of April, 1932. She withstood the operation successfully and remained free from syncopal attacks for the ensuing 2 months, when their reappearance compelled her to enter the Beth Israel Hospital on June 16, 1932. She remained at that institution for almost 1 month when her Stokes-Adams seizures became less frequent and finally disappeared entirely before she was discharged.

On January 18, 1933, she began to experience recurrent syncopal attacks lasting several minutes at a time. On the following day she died following one of these long seizures.

Cardiac Mechanism. While she was under observation, repeated electrocardiograms were taken. These were correlated with her clinical manifestations and they showed an unsual and unique sequence of events. Her basic rhythm alternated for long periods

at a time between that of a normal sinus rhythm and auriculoventricular dissociation. The normal sinus rhythm was characterized graphically (most of these studies were carried out with Lead II only and unless otherwise specified, comparisons are made of complexes in this lead only) by an upright auricular complex with a *P-R* interval measuring 0.16 second and a notched ventricular complex 6 mm. in height and 0.16 second in width (Fig. *A*-1). At such times the auricular and ventricular rates averaged 100 beats per minute. Sooner or later the basic ventricular rate of the sinus rhythm was halved (Fig. *A*-2). It will be observed that this halving was due to what appears to be blocked auricular beats. However, the *P-R* interval following a blocked auricular beat (Fig. *A*-2-2*B*) is shorter than the one preceding the basic ventricular complex (Fig. *A*-2*A*) and the main ventricular deflection following the shortened *P-R* interval is different in size, shape, and form from the usual complexes.

For hours at a time the auricular as well as the ventricular rates, in the presence of auriculoventricular dissociation, were unusually labile. At times the auricles beat at the rate of 120 beats per minute and a bigeminal rhythm resulted (Fig. *A*-3), when the electrocardiograms revealed an apparent 3 :2 block, 3 auricular contractions being present to every 2 ventricular contractions. A slowing of the ventricular rate to 54 beats per minute was accompanied by an auricular rate of 100 beats (Fig. *A*-4).

Suddenly the ventricles would slow to 46 beats (Fig. *A*-5) and the auricles to 89 before they would accelerate again to 100 or 120 beats (Fig. *A*-6, 7) and the ventricles to 54 or 60 beats. At such intervals the shape of the *T* waves would be altered by the superimposed auricular deflections although the main ventricular deflections would hardly be altered.

Frequently, a 3 :2 block would occur with a regular auricular rate of 90 and the ventricles beating at 46 per minute (Fig. *A*-9) before a further slowing of both the auricles and the ventricles would be interrupted by extrasystoles (Fig. *B*-1*A*) of a peculiar type, preceded by a shortened *P-R* interval.

At first these single extrasystolic contractions, which increased the rate of the heart beats during the presence of auriculoventricular dissociation, could all be heard over the apical region of the heart and could be felt at the pulse. The bigeminal rhythm could not, however, be distinguished from that produced by the alternate presence of 3 auricular contractions described above (Fig. *A*-3).

The ventricular complex of the first beat of the bigeminy, due to alternate premature ventricular contractions, was usually similar to the ventricular complex present when there were blocked auricular beats (cp. Fig. *B*-4*A* and 4*B* with Fig. *A*-2*A* and 2*B*). At other times it differed and resembled the basic ventricular complex observed during sinus rhythm.

Occasionally this bigeminal rhythm consisted of an allorhythmia in which a normal sinus beat followed by a premature ventricular contraction (Fig. *E-2A*) appeared periodically after each eighth ventricular contraction (Fig. *E-2A, B, C*). Each bigeminal group consisting of a normal sinus beat and an extra systole was followed

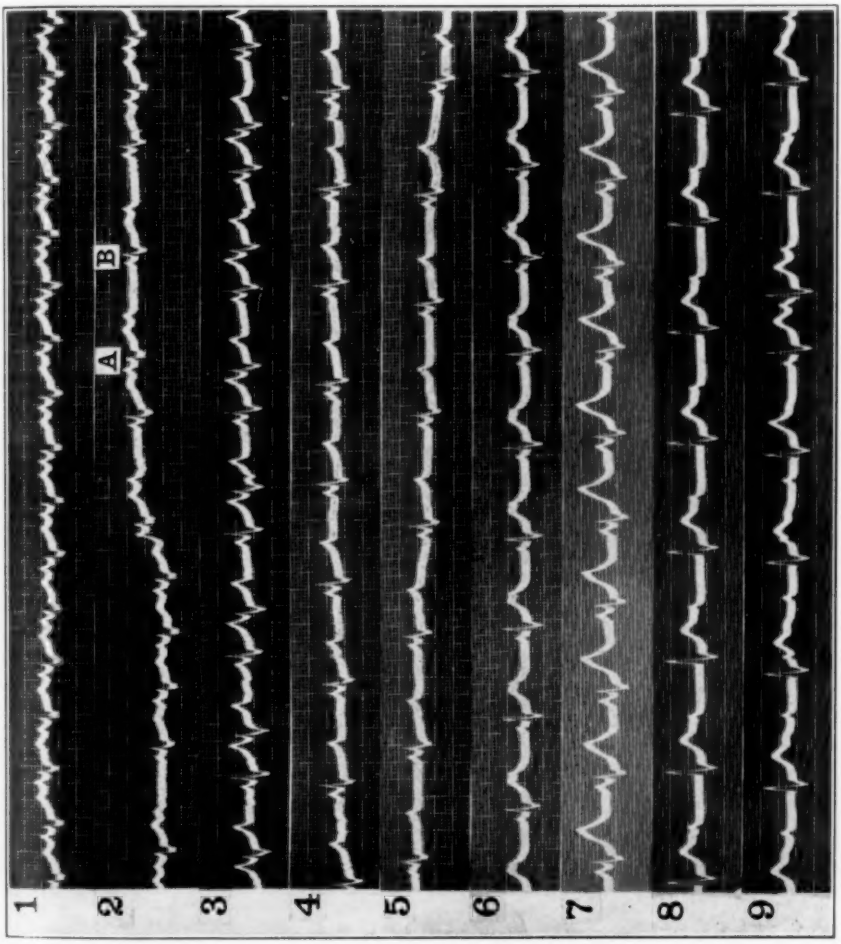


FIG. A.—(1) The basic sinus rate is 100 beats per minute. (2) Both the *P* and *Q-R-S* complexes of the basic sinus rhythm are different from those present during transient auriculoventricular dissociation. (3) 3 to 2 block (4, 5, 6, 7, 8, 9). The rate of the auricles as well as that of the ventricles waxes and wanes during established auriculoventricular dissociation.

by a series of bigeminal beats in which the first complex was idioventricular, without any definite auricular wave or *P-R* interval preceding it and it was totally different in size, shape, and form from the basic ventricular complex.

This would indicate that the heart was under the control of two different centers acting independently of each other, each one send-

ing out impulses of its own, one impulse originating in the sinus node and the other in the auriculoventricular node or in the tissues adjacent to it.

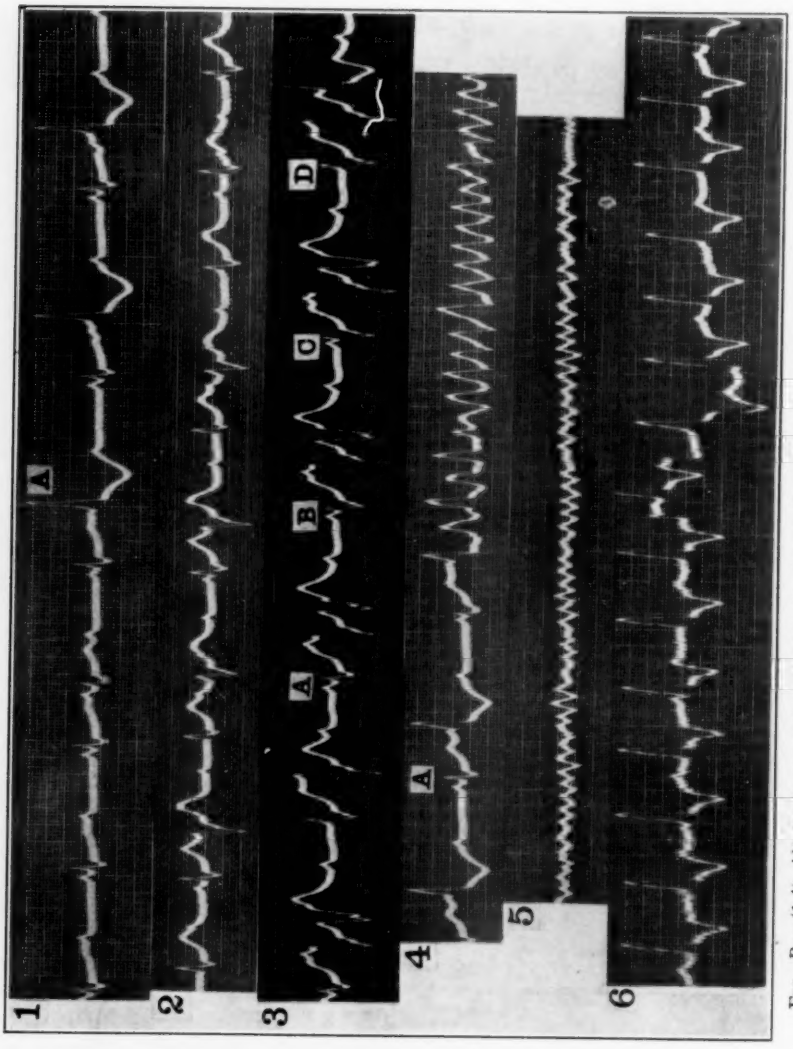


FIG. B.—(1,4) Alternate premature ventricular beats disrupting the basic heart rhythm which consists of a 2 to 1 heart block. (2) The auricular and ventricular rates increase independently of each other after the appearance of premature ventricular beats. (3A, B, C, D) The basic ventricular complex changes periodically, this change depending in part upon its distance from the preceding auricular complex. (4A) Recurrent ventricular oscillations associated with ineffectual ventricular contractions may appear when the rhythm of the heart is slow. (5) Record obtained during a Stokes-Adams seizure. (6) The postfibrillatory period.

Sometimes the shape of the basic ventricular complex would change from beat to beat especially when, to the bigeminal rhythm, there would be added from time to time, one or more recurrent ventricular oscillations. These ventricular oscillations which ap-

peared in an unpredictable manner, were aberrant in form and only the first two or three could be heard at the apical region of the heart or felt at the pulse. The shape of the basic ventricular complex was dependent at such times upon the distance of the preceding

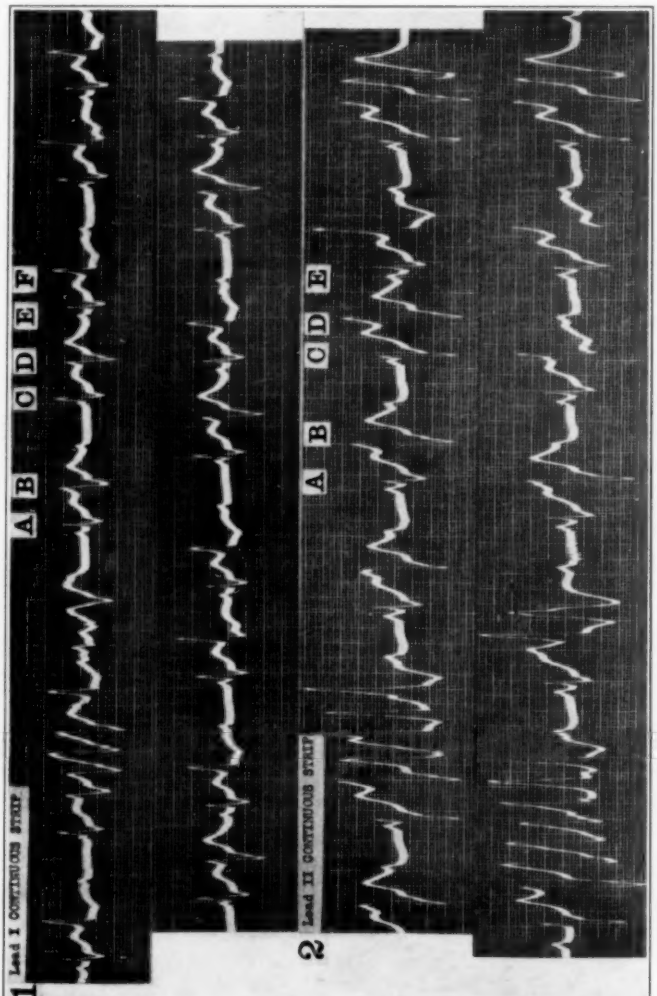


FIG. C.—1C, D, E, F; 2C, D, E, F) A quadrigeminal rhythm interrupting the basic rhythm. A nodal beat (C) is followed by a premature ventricular beat (D). Then a normal beat (E) is also followed by a premature ventricular beat.

P wave from it (Fig. *B-3A*, *B*, *C*, *D*). As the *P-R* interval became shorter and shorter, the ventricular complexes became larger and more aberrant. The likelihood of a shift of the pacemaker of the heart from the sinus node to the auriculoventricular node offers the most logical explanation for this phenomenon. This change in

the basic ventricular complex, however, did not alter the shape or rhythm of the additional recurrent ventricular oscillations that would follow it.

As the recurrent ventricular oscillations following a basic ventricular complex increased in frequency, the fundamental mechan-

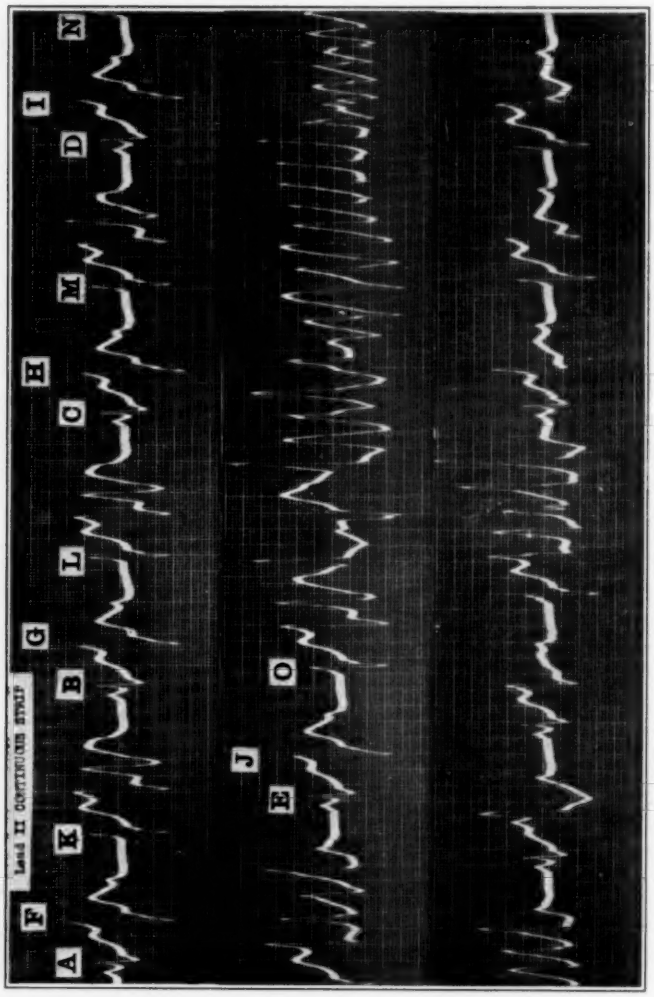


FIG. D.—An allorhythmia consisting of a normal beat (*A, B, C, D, E*), a premature beat (*F, G, H, I, J*), and a nodal beat (*K, L, M, N, O*) precedes a short run of ventricular fibrillation (*O*).

ism of the heart assumed a quadrigeminal rhythm which lasted for minutes or sometimes hours at a time (Fig. *C*-1*C*, *D*, *E*, *F*; 2*C*, *D*, *E*, *F*). This rhythm could be appreciated clinically. The four beats making up this quadrigeminy consisted of a nodal ventricular complex (Fig. *C*-1*C*, 2*C*) preceded by a very shortened *P*-*R*

interval and a positive auricular complex, part of which was buried in it. This was followed by a premature ventricular contraction (Fig. *C*-1 *D*, 2 *D*) which in turn was succeeded by a normal basic

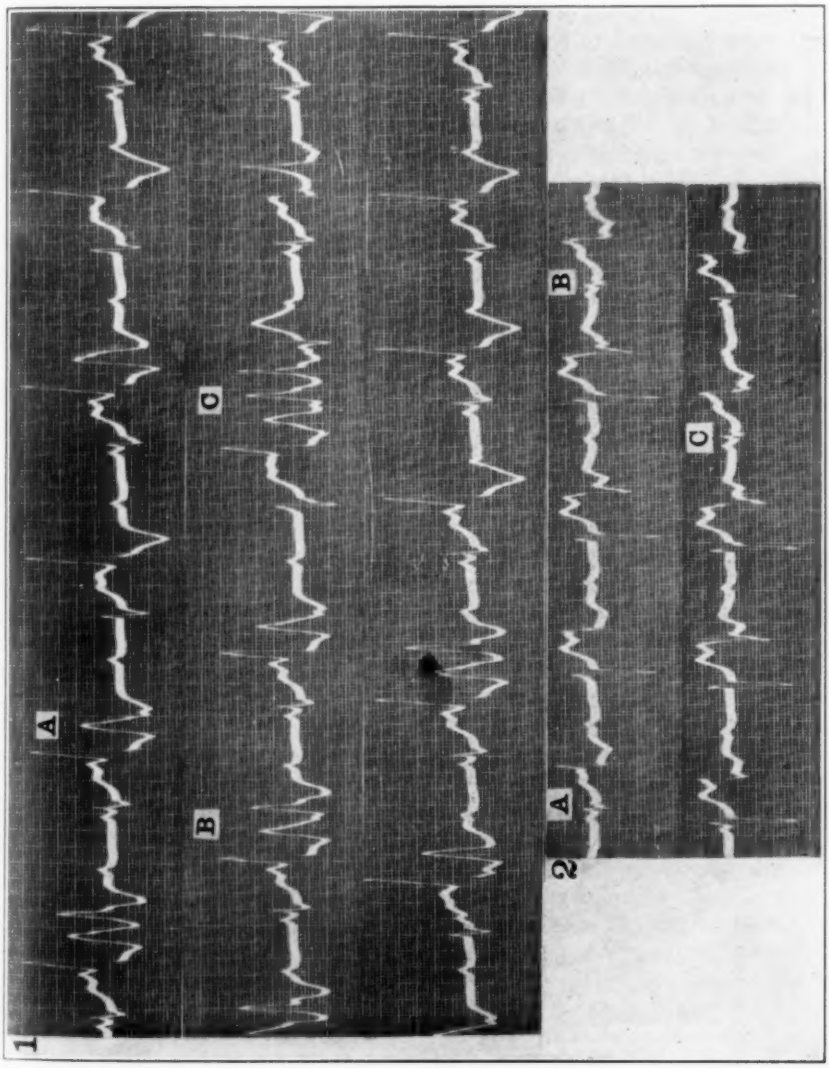


FIG. E.—(1 *A*, *B*) Recurrent ventricular oscillations may appear after a normal sinus beat or after an idioventricular beat (*C*). (2 *A*, *B*, *C*) A normal sinus beat appears as the 8th ventricular contraction. This rhythm preceded all other allorhythmias encountered in this patient prior to syncopal seizures.

ventricular complex that followed an upright auricular wave with a *P*-*R* interval of 0.16 second, similar to that observed during normal sinus rhythm. This normal beat was followed by another premature ventricular contraction, which made up the last element of the

quadrigeminy. The four grouped beats were separated from other similar ones by an interval measuring almost 0.8 second (cp. Fig. *C*, 1 and 2).

In the mean time, as these allorhythmias were appearing and alternating with other variations in the rhythm of the heart, the patient's clinical condition was not affected. She was conscious of an occasional precordial thump but aside from that, the circulation was adequately maintained. It was not until these abnormal alterations in the rhythm were further disrupted by the addition of recurrent ventricular oscillations appearing in groups of three or more, that the patient began to complain. These additional recurrent ventricular oscillations could be appreciated clinically by the appearance of "pulse pauses" which resulted from the absence of effectual ventricular contractions, since they were frustrane in character and too weak to open the aortic orifice.

It was impossible to predict in any way the appearance and duration of these "pulse pauses." Sometimes they were ushered in when the basic rhythm of the heart was slower (Fig. *E*-1*A*, *B*, *C*), while at other times when it had been accelerated by the addition of multiple premature ventricular beats (Fig. *C*-1). At no time, however, in the hundreds of records obtained of these alterations in rhythm preceding a major syncopal seizure were any runs of these ventricular oscillations initiated abruptly without the presence of some of the preliminary events described above.

More often, before a major syncopal attack, the cardiac mechanism consisted of an allorhythmia in which the basic ventricular deflection (Fig. *D*-*A*, *B*, *C*, *D*, *E*) was preceded by a normally shaped auricular complex with a *P*-*R* interval measuring 0.16 second. This was followed at an interval of 0.36 second by a premature ventricular beat (Fig. *D*-*F*, *G*, *H*, *I*, *J*). This bigeminal rhythm, with almost constant regularity, was in turn followed by two aberrant ventricular complexes (Fig. *D*-*K*) and sometimes by many more (Fig. *D*-*N*). (Cp. this mechanism with that of Fig. *C*.)

The "initial" ventricular complex ushering in the recurrent ventricular oscillations was usually opposite in direction to its preceding beat. It followed a basically normal ventricular complex or a nodal or idioventricular beat. This "initial" beat was most often of the same size and shape and form but its succeeding complexes were extremely variable. They were aberrant, bizarre, changed from beat to beat at times, and showed no definite base line. Frequently, they changed abruptly in duration and direction and would or would not be ended by a postundulatory pause. The auricular beats could not be made out during their presence, although the rate and sequence of the auricular beats was not disturbed.

The clinical manifestations associated with these recurrent ventricular oscillations depended upon their duration at any one time and resembled in every respect the signs and symptoms observed in other patients in whom their persistence for over 40 seconds

resulted in a typical Stokes-Adams seizure with unconsciousness, epileptiform convulsions, stertorous breathing ending in apnea, and intense cyanosis which disappeared with the first effectual contractions that initiated spontaneous revival of the heart.

The period following immediate revival of the heart consisted of an intermediary idioventricular rhythm with a rapid irregular idioventricular rate that slowed after several minutes to either the sinus rhythm or the allorhythmia which preceded the onset of syncope during established auriculoventricular dissociation.

Discussion. The accompanying electrocardiograms reveal the successive alterations in the rhythm of the heart preceding syncopal seizures in this woman to have consisted at first of the development of transient auriculoventricular dissociation, so that a normal heart rate of 100 beats per minute was slowed to one-half its original. The transition from a normal rhythm to a halved one was not abrupt but gradual and there were alternating periods of normal sinus rhythm with dissociation for some time before dissociation persisted. There was a marked waxing and waning of both the auricular and ventricular rates during the presence of established dissociation of the auricles from the ventricles. An acceleration or retardation of the auricles did not influence, however, the ventricular rate or *vice versa*.

It is not within the province of this study to give a detailed explanation of the mechanism responsible for the various allorhythmias encountered in this patient. It will suffice to state that the occasional recurring and periodic presence of a normal sinus beat during established auriculoventricular dissociation indicates that the heart during such periods was activated by two centers, each sending out impulses of its own, one superceding the other by virtue of changes in the refractoriness of the auriculoventricular node and bundles resulting in a so-called para-arrhythmia[2] with interference and dissociation.[3]

All of these variations in the rhythm of the heart yielded an acceleration of the ventricular rate during block and it is very likely that this increase in the ventricular rate is a very necessary precursory mechanism in the development of the subsequent changes that precede ventricular fibrillation. For an increase in the ventricular rate above that of the usual basic rate has already been observed in other patients with similar symptoms and signs. (Preceding article.)

Of greater importance, in addition to the increase in the ventricular rate, is the fact that a major syncopal seizure was invariably heralded by the appearance of short runs of ventricular oscillations, which in their final analysis turn out to be short runs of ventricular fibrillation.[4] It is their presence in the electrocardiograms which predicates longer runs of a similar nature that finally result in syncope. Since no other types of syncopal seizures have been observed to be preceded by similar events in the cardiac mechanism, it is fair to assume that these recurrent groups of ventricular oscilla-

tions are pathognomonic for syncope associated with ventricular fibrillation.

Summary and Conclusions. 1. Successive electrocardiograms were correlated with the clinical manifestations of a woman who was suffering from recurrent syncopal seizures. Particular attention was paid to the alterations in the rhythm of the heart that preceded syncope.

2. The patient usually showed normal sinus rhythm in between attacks. For some time prior to a seizure, the normal sinus rhythm alternated with that of auriculoventricular dissociation.

3. There was a marked waxing and waning of the rates of both the auricles and ventricles during the presence of auriculoventricular dissociation.

4. Sooner or later this dissociated rhythm would be interrupted by premature ventricular beats coming on singly so as to form a bigeminal rhythm. Occasionally a normal sinus beat would be interpolated in this dissociated rhythm, appearing at first after every 8th effectual ventricular contraction and then more frequently. Alterations between the normal sinus rhythm and the dissociated rhythm resulted in grouped beats forming trigeminies and quadrigeminies with regular periodicity.

5. When the appearance of these various rhythms had materially increased the rate of the ventricles after they had been slowed during auriculoventricular dissociation, recurrent ventricular oscillations began further to disrupt the cardiac mechanism.

6. These aberrant ventricular oscillations were variable in shape, size, and form from beat to beat. They were associated clinically with ineffectual ventricular contractions resulting in periodic "pulse pauses," absent heart sounds, and a collapse of the circulation.

7. If these ventricular oscillations lasted from 8 to 10 seconds, then the patient merely shut her eyes and her face assumed an ashen gray pallor. If they were of 20 seconds, duration she lost consciousness. If they lasted longer than 40 seconds a typical Stokes-Adams seizure ensued.

8. These short groups of ventricular oscillations are short runs of ventricular fibrillation and no syncopal seizure resulting from ventricular fibrillation appeared without these shorter runs heralding a major attack. Because of this, they are pathognomonic for ventricular fibrillation and their recurrent presence in any electrocardiogram should help in the diagnosis of the cardiac mechanism underlying such syncopal seizures.

BIBLIOGRAPHY.

1. Schwartz, S. P.: Arch. Int. Med., 1932, **49**, 282.
Schwartz, S. P., and Jezer, A.: Ibid., 1932, **50**, 450.
2. Kaufman, R., and Rothberger, C. J.: Ztschr. f. d. ges. exper. Med., 1920, **11**, 40.
3. Mobitz, W.: Ibid., 1923, **34**, 490.
4. Schwartz, S. P., and Jezer, A.: Am. J. Med. Sci., 1934, **187**, 469.

CLINICAL EVALUATION OF LEAD IV (CHEST LEADS).

A Survey of Lead IV in Ambulatory Cases of Coronary Artery Disease and Acute Coronary Occlusion.

By A. Allen Goldbloom, M.D., F.A.C.P.,
adjunct physician in medicine, beth israel hospital, new york city.

Any clinical method that promises a possibility of arriving at more exact diagnosis deserves attention. This is especially true if the method is not cumbersome and can be used in both office practice and at the bedside.

In 1932, Wolferth and Wood[1] published the results of a study of Lead IV as an electrocardiographic aid in the diagnosis of coronary occlusion. A number of authors since that time have reported their findings with this method, namely, Lieberson and Liberson,[2] Katz and Kissin,[3] and Hoffman and Delong.[4] To date, however, the cases reported have been mainly hospital cases, presenting definite clinical evidence of coronary artery disease, with or without occlusion.

The series reported herein have been chosen from private practice. All the 86 patients were ambulatory except 13, who were studied with the aid of a portable electrocardiograph, first at home during an acute attack and later in the office. Forty of the 86 patients had definite clinical symptoms of coronary artery disease, with or without a history of acute occlusion. Some of these 40 had a symptom complex of angina pectoris. In addition 8 non-coronary cardiac cases and 25 non-cardiac cases for control were studied.

The purpose of the study was to see whether Lead IV would be positive only in those cases where the routine 3 leads were positive, or whether it might sometimes be positive while the routine 3 leads were negative. If the 4th lead were positive only in conjunction with positive routine 3 leads, it would be superfluous as an additional method; but if it should prove positive in any case where the routine 3 leads were negative or doubtful, it would be of definite value.

The Method. The method of Wolferth and Wood was carried out, after employing the method customarily used for the routine 3 leads. The cardiac region anteriorly and the spinal region medial to the right scapula posteriorly were thoroughly scrubbed with warm saline water to make these areas hyperemic. The electrodes were held firmly in place over the corresponding areas by bandaging the patient's chest tightly. The lead wire of the right arm was connected to the plate anteriorly, while that of the left arm was connected posteriorly. Those cases in whom the arm leads were reversed, as mentioned by Wolferth and Wood, and carried out by Lieberson and Liberson, are designated in our series by the letter B. We did not find it necessary to shave the skin or hold the plates by a special paste as advocated by Katz and Kissin, or to utilize special electrodes as suggested by Hoffman and Delong.

Normal Lead IV. Fig. 1 shows the variation of complexes found in the 25 normal control cases. Most of the complexes show a negative *P* wave. The *Q–R–S* complexes are diphasic, with a definite deep *Q* wave and inverted *T* wave. The *T* waves are inverted in most cases and diphasic in only 2 (Cases 323 and 332). The depth of the *T* wave varies from 2 to 9 mm., the average depth being 4.9 mm. (Table 1).* The *Q–R–S* complexes are not slurred and are slightly higher than in the routine 3 leads. By reversing the arm leads, as in Case 508*B*, a reverse image of the above complexes is seen. In the reverse position, the *T* waves are upright and there is an *S* wave in place of the deep *Q* wave. When interpreting Lead IV electrocardiograms, one must be careful to remember the method employed, an inverted *T* wave being normal in the anteroposterior position.

TABLE 1.—AVERAGE DURATION AND HEIGHT OF COMPLEXES IN NORMAL LEAD IV.

Case No.	Height of *P* waves, mm.	*P–R* interval, sec.	*Q* complex, mm.	*Q–R–S* complexes. Height, mm.	*Q–R–S* complexes. Width, sec.	*T* waves, mm.
323	−1	0.16	−3	+9	0.08	−2
332	−1	0.12	−5	+18	0.08	−3
351	−1	0.16	−10	+12	0.08	−8
361	+1	0.12	−10	+15	0.08	−4
417	+1	0.12	−6	+18	0.08	−6
428	0	0.12	−7	+12	0.08	−7
429	−1	0.16	−7	+13	0.04	−6
430	−1	0.16	−5	+15	0.08	−6
432	−1	0.16	−4	+15	0.04	−6
440	−1	0.16	−5	+14	0.08	−5
441	−1	0.12	−6	+13	0.08	−4
447	−1	0.12	−4	+11	0.08	−3
450	−1	0.12	−5	+12	0.08	−6
473	+1	0.12	−7	+11	0.08	−4
475	−1	0.12	−8	+9	0.04	−4
476	−1	0.16	−14	+13	0.08	−6
478	−1	0.12	−10	+7	0.12	−8
482	−1	0.12	−10	+7	0.08	−3
483	−1	0.12	−9	+9	0.12	−7
493	−1	0.16	−9	+9	0.08	−5
495	−1	0.16	−6	+6	0.04	−2
497	−2	0.12	−5	+10	0.08	−3
498	−2	0.12	−8	+9	0.12	−5
506	+1	0.12	−10	+10	0.08	−5
507	−1	0.12	−7	+9	0.04	−5
Average	−0.6	0.134	−7.2	+10.8	0.076	−4.9

Lead IV in Coronary Artery Disease With Myocardial Damage. Forty of our cases came to the office complaining of what they thought was a gastro-intestinal disturbance. Inquiry revealed that the symptoms were most probably due to coronary artery disease; in several cases, there was actually a definite history of an acute

* Acknowledgement is hereby gratefully given Mr. Paul K. Roht for his assistance in preparing the tables.

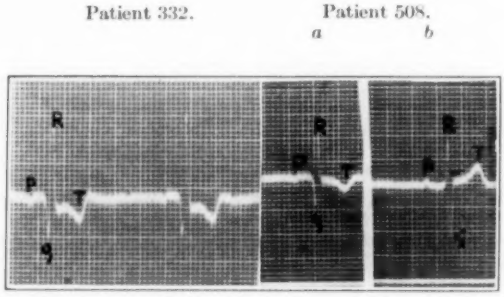


FIG. 1.—Types of normal Lead IV. *a*, Anteroposterior position; *b*, posteroanterior position.

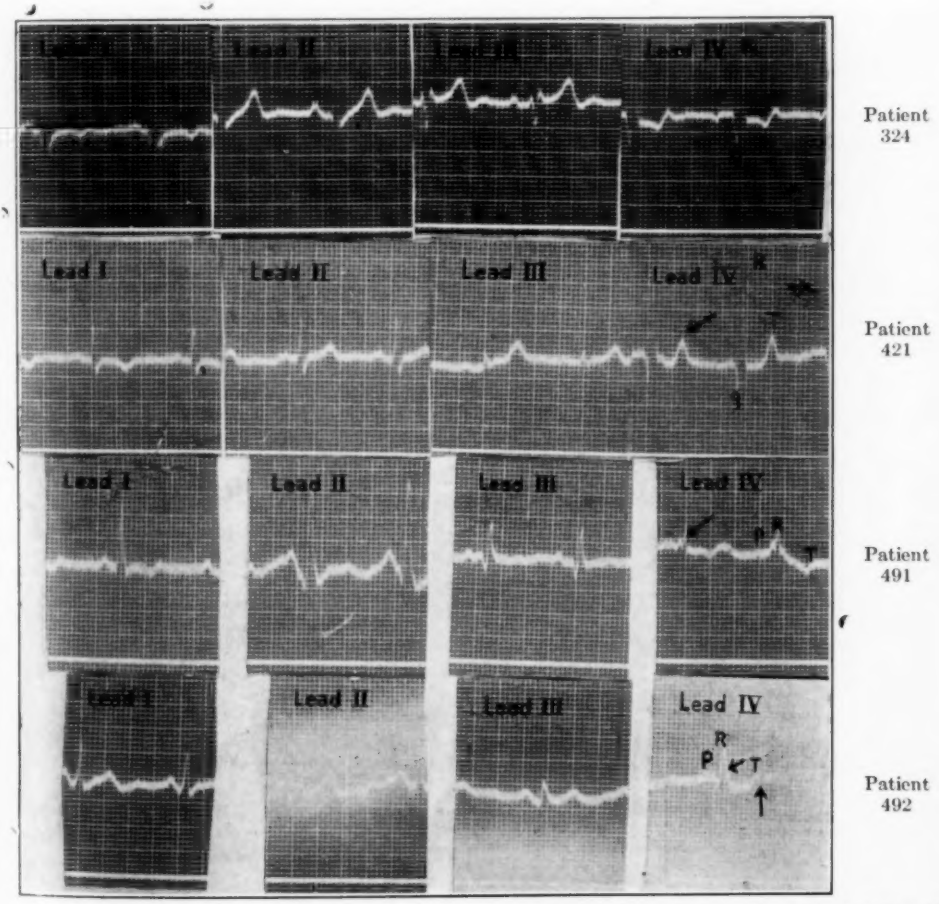


FIG. 2.—Cases of coronary artery disease, showing the routine three leads with variant types of Lead IV (normal and abnormal).

TABLE 2.—AVERAGE DURATION AND HEIGHT OF COMPLEXES IN LEAD IV OF CORONARY ARTERY DISEASE. COMPARATIVE EVALUATION OF THE ROUTINE THREE LEADS AND LEAD IV.

Case No.	Height of *P* waves, mm.	*P–R* interval, sec.	*Q* complex, mm.	*Q–R–S* complex.		*T* waves, mm.	Blood-pressure.	Lead I.	Lead II.	Lead III.	History.	Evaluation of routine leads.	Lead IV.
				Height, mm.	Width, sec.								
324	−1	0.16	−7	+15	0.08	−2	140/80	Diphasic T_1	.....	T_3 above line	+	+	−
349	−1	0.12	−6	+17	0.08	−2	96/60	.....	.....	.....	+	−	−
352	−1	0.12	−7	+16	0.08	+2	90/60	T_1 above line, slurring	T_2 above, slurring	Low, slurring	+	+	+ slurring.
355	−1	0.16	−9	+7	0.08	−6	130/80	Slurring	Slurring	Q_3 deep, slurring	+	+	−
372	0	0.16	−10	+7	0.08	−5	90/60	.....	T_2 diphasic	Inverted	+	+	−
376	−1	0.16	−9	+9	0.08	−5	160/90	.....	T_2 upright	T_3 inverted	+	−	−
402	−1	0.16	−7	+15	0.04	−3	130/80	Slurring	Slurring	Slurring	+	+	−
407	+1	0.16	−1	+4	0.08	0	130/80	T_1 inverted	T_2 above	T_3 above line	+	+	−
418	−1	0.16	−15	+15	0.08	−5	160/90	.....	Slurring	.....	+	−	−
420	−1	0.12	−9	+15	0.08	−2	110/60	.....	Slurring	Q_3 deep	+	+	−
421	0	0.12	−4	+15	0.08	+4	120/90	T_1 inverted, slurring	Slurring	T_2 above line, slurring	+	+	−
423	−1	0.12	−9	+15	0.08	−2	140/80	.....	T_2 down	Q_3 deep	+	+	+
424	+1	0.16	−2	+15	0.04	+2	138/70	Slurring	T_2 diphasic, slurring	T_2 above line, slurring	+	+	+
426	−1	0.12	−8	+15	0.08	−4	80/60	.....	.....	Q_3 deep	+	+	−
433	+1	0.12	−3	+10	0.08	−2	110/70	.....	.....	.....	+	−	+ slurring.
434	−1	0.16	−10	+15	0.08	−1	100/70	.....	.....	.....	+	−	−
436	−1	0.12	−8	+10	0.08	−3	110/70	.....	.....	Q_3 deep	+	+	+ slurring.
438	−1	0.16	−7	+12	0.04	−3	100/60	.....	.....	.....	+	−	+
443	−1	0.12	−5	+11	0.08	−6	130/80	.....	.....	Q_3 deep	+	+	+
448	−1	0.16	−5	+10	0.04	−3	160/80	.....	.....	Q_3 deep	+	+	+
451	−1	0.16	−10	+12	0.08	−4	130/80	.....	.....	Q_3 deep	+	+	−
454	−1	0.12	−7	+9	0.08	−6	110/80	Slurring	Slurring	Slurring	+	+	+
471	+1	0.12	−7	+9	0.08	−6	120/80	T_1 slurring, upright	T_2 diphasic, slurring	T_3 inverted, slurring	+	+	−
459	−1	0.12	−10	+12	0.04	−3	180/90	T_1 diphasic	T_2 diphasic	T_3 diphasic	+	+	−
460	−1	0.16	−10	+15	0.08	−6	140/80	.....	.....	.....	+	−	−
467	−1	0.12	−9	+14	0.08	+3	115/90	T_1 inverted	.....	Q_3 deep	+	+	−
468	+1	0.12	−10	+10	0.08	−7	120/80	.....	T_2 above line	T_3 above line	+	+	−
470	−1	0.12	−9	+19	0.04	−3	135/90	.....	.....	.....	+	−	−
474	−1	0.16	−10	+7	0.08	−2	130/80	Slurring	Slurring	Q_3 deep, slurring	+	+	−
480	0	0.10	−5	+7	0.08	−7	130/80	Slurring	Slurring	T_3 above, slurring	+	+	+
484	−1	0.16	−9	+10	0.08	−7	110/80	.....	.....	Q_3 deep	+	+	+
488	+1	0.12	−9	+12	0.08	−4	90/60	T_1 diphasic	.....	T_3 above	+	+	−
490	−1	0.12	−9	+15	0.08	−9	150/90	T_1 above line	T_2 below	T_3 below	+	+	−
491	+1	0.12	0	+4	0.08	−2	120/60	T_1 inverted, slurring	T_2 diphasic, slurring	T_3 poor	+	+	−
492	+1	0.12	0	+8	0.08	−1	110/70	.....	.....	.....	+	−	+
494	0	0.12	−3	+10	0.08	−2	90/50	T_1 above line	T_2 above	T_3 diphasic	+	+	+
496	−1	0.16	−9	+10	0.04	−7	130/80	.....	.....	.....	+	−	−
500	−1	0.16	−9	+10	0.08	−9	160/60	Small complexes	Small complexes	Small complexes	+	+	−
509	−1	0.12	−9	+8	0.08	−5	140/90	.....	.....	.....	+	−	−
510	−1	0.12	−8	+8	0.08	−3	160/90	T_1 diphasic	T_2 diphasic	.....	+	+	−
Av.	−0.5	0.13	−7.3	+11	0.07	−3.4							

coronary occlusion which had been erroneously interpreted by the patient as an attack of acute indigestion.

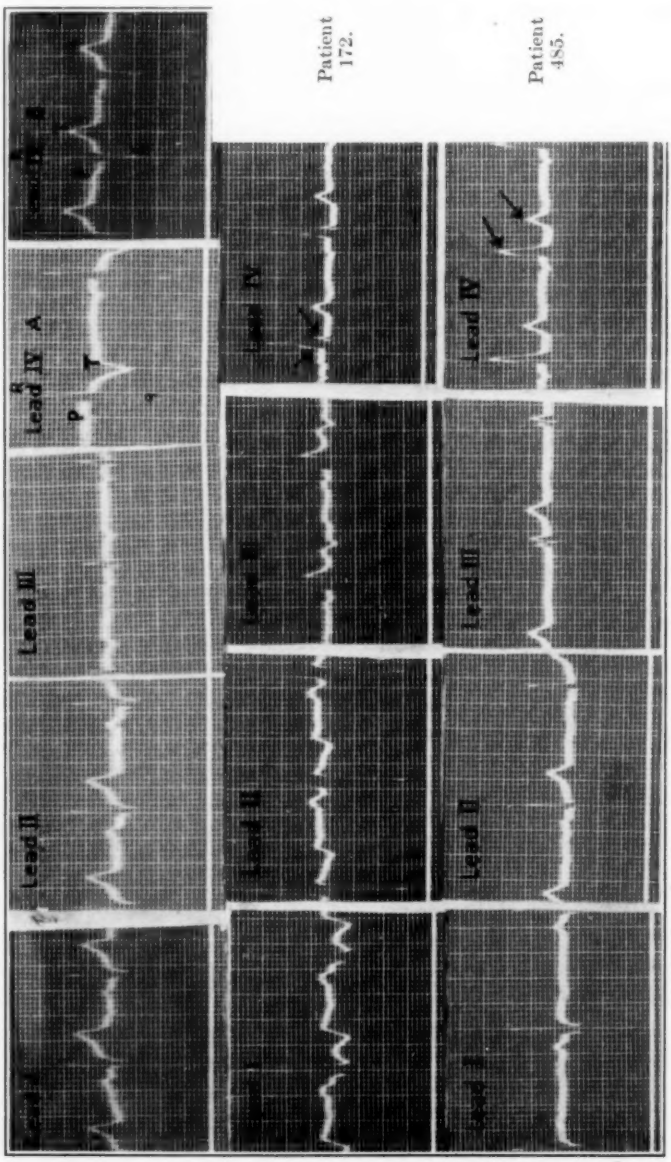


FIG. 3.—Cases of acute coronary occlusion, showing normal and abnormal Lead IV.

Table 2 shows that in these 40 cases there is practically no deviation in the width or height from the complexes of the 25 nor-

mal control patients. By "positive history" in the table is meant subjective complaints of precordial pain, with or without radiation, dyspnea, and other classical symptoms. By "routine leads" is meant findings in Leads I, II and III sufficiently characteristic to

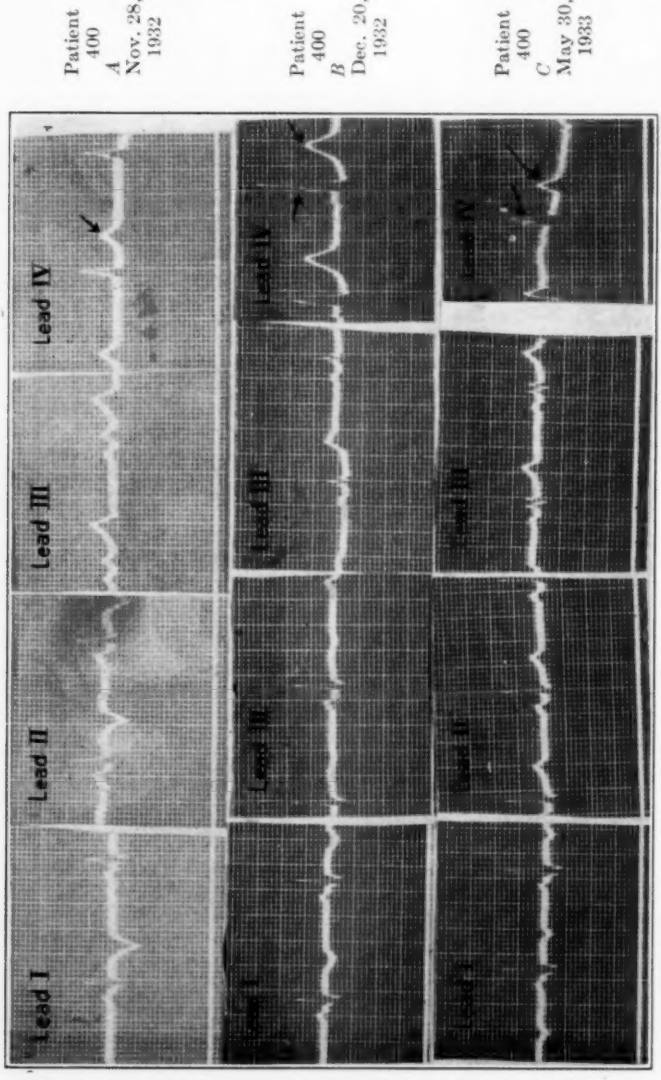


FIG. 4.—Serial electrocardiograms in a case of acute coronary occlusion showing a persistently abnormal Lead IV.

make the electrocardiogram positive for myocardial damage due to coronary artery disease. A "plus sign" under Lead IV indicates some abnormal finding, making this lead of value in substantiating the clinical diagnosis.

Routine Leads I, II and III are to be considered positive only where the following findings are present: A high take-off of the *T* waves above the isoelectric line; diphasic *T* waves in more than 1 lead; slurring of the *Q–R–S* complexes in all leads; small complexes in all leads; and a deep Q_3 wave, the value of which as a positive finding we[5] recently emphasized.

Lead IV is to be considered abnormal when it varies from Lead IV in the control series, either in the direction of the complexes, as marked slurring of the *Q–R–S* complexes (Fig. 2, Case 491), also when *Q* or *T* waves are absent (Fig. 2, Case 492) or when there is an upright *T* wave (Fig. 2, Case 421). Slurring of the *Q–R–S* complexes in Lead IV is indicative of a lesion, since it is not always found in routine Leads I, II and III. In 5 cases, slurring of the *Q–R–S* complexes is present in all 4 leads, while in 5 it is present only in Lead IV. The diphasic *T* wave in Lead IV (Case 324, Fig. 2) is not to be considered abnormal, since it is also encountered in Lead IV of normal patients (Case 332, Fig. 1). An inverted *T* wave to 9 mm. in depth is not considered pathologic, inasmuch as it is found in normal cases. The average depth in these cases of the inverted *T* wave is 3.4 mm. Katz and Kissin consider inverted *T* waves of 9 mm. or more as pathologic, but since we encountered inverted *T* waves of 9-mm. depth in both normal and abnormal cases, we regard it as a doubtful indication of a lesion.

Of the 40 cases of coronary artery disease with myocardial damage, the routine 3 leads are positive in 28 cases (70 per cent). Twelve cases show an abnormality in Lead IV and positive routine 3 leads (30 per cent). Three cases, however (Nos. 433, 438 and 492, Table 2) show an abnormal Lead IV, but negative Leads I, II and III (7.5 per cent). The diagnosis of coronary artery disease with myocardial damage is, therefore, definitely aided by Lead IV in 7.5 per cent of cases.

Non-coronary Cardiac Cases. Eight cases of non-coronary cardiac disease were studied, 3 of whom were cases of mitral valvular disease (rheumatic), 2 auricular fibrillation (hypertensive), 1 intraventricular block and 1 hyperthyroid. In this group, Lead IV shows nothing of significance. This is interesting, as Hoffman and Delong reported abnormal Lead IV in a case of rheumatic mitral stenosis and in a luetic cardiac case.

Lead IV in Acute Coronary Occlusion. Thirteen of our series were first seen at the bedside at home during or within the first few days of an acute attack of coronary thrombosis. The history as well as the clinical symptoms and signs were characteristic, so that there was no question as to the clinical diagnosis. The electrocardiogram substantiated the diagnosis of the presence of the so-called coronary *T* wave of Pardee[6] or the cove *T* wave as described by Rothschild, Mann and Oppenheimer.[7] These criteria have been utilized as designating the routine 3 leads as positive (Table 3), in substantiat-

TABLE 3.—THE EVALUATION OF LEAD IV AND ROUTINE THREE LEADS IN CASES OF ACUTE CORONARY THROMBOSIS.

Case No.	Height of *P* waves, mm.	*P–R* interval, sec.	*Q* complex, mm.	*Q–R–S* complex.		*T* waves, mm.	Blood-pressure.	Lead I.	Lead II.	Lead III.	History.	Evaluation of routine leads.	Lead IV.
				Height, mm.	Width, sec.								
172	−1	0.12	0	+16	0.08	+3	110/80	T_1 diphasic	T_2 diphasic	T_3 above	+	+	+
190	+2	0.16	−16	+15	0.08	−7	120/80	T_1 above	T_2 above	Slurred	+	+	−
299	−1	0.12	−15	+10	0.08	−10	90/60	T_1 above	T_2 above	T_3 inverted	+	+	−
350	−1	0.12	−15	+15	0.08	−8	90/60	T_1 above	T_2 above	T_3 inverted	+	+	−
362	−1	0.12	−11	+14	0.08	−7	90/60	T_1 cove	T_2 cove	T_3 cove	+	+	+
371	−1	0.12	−6	+10	0.08	+3	100/70	T_1 inverted	T_2 high	T_3 high	+	+	+
374	0	0.16	0	+5	0.08	0	120/80	T_1 upright	T_2 upright	T_3 diphasic	+	−	+
400	0	0.12	0	+9	0.08	+4	120/70	T_1 cove	T_2 cove	Slurred	+	+	+
422	+1	0.12	−6	+7	0.08	+3	150/100	T_1 diphasic	T_2 diphasic	T_3 inverted	+	−	+
427	+1	0.12	−2	+9	0.04	+2	136/80	Poor	T_2 above	Q_3 deep	+	+	+
485	−1	0.12	0	+13	0.08	+6	130/90	T_1 inverted	T_2 above	T_3 above	+	+	+
489	−1	0.16	0	+17	0.08	+3	100/74	T_1 inverted	T_2 absent	T_3 upright	+	−	+
504	−1	0.16	0	+4	0.08	+3	80/50	Slurring	T_2 inverted	Slurring	+	−	+
Av.	−0.30	0.12	−6.2	+11	0.073	+3							

ing the clinical diagnosis of acute coronary occlusion. Inverted or diphasic *T* waves do not seem sufficient to designate the routine leads as "positive" for acute coronary occlusion. In 9 of the 13 cases (69 per cent), the routine 3 leads are positive for acute coronary occlusion. Lead IV shows evidence of some abnormality in the remaining 4 cases (Cases 374, 422, 489, and 504 Table 3), namely, marked slurring of the *Q–R–S* complexes, upwardly directed *T* waves or an absent *Q* wave. In the 3 cases of acute coronary thrombosis (Cases 190, 299 and 350, Table 3), where Lead IV is negative, the complexes are similar in form to those found in normal Lead IV cases.

Fig. 4, Case 400, represents a serial electrocardiogram; 400*A* shows a definite cove *T* wave in Leads I and II, taken 24 hours after the onset of the acute attack. Lead IV shows slight slurring of the *Q–R–S* complexes and a definitely upwardly directed *T* wave. Following this case, it is apparent that the cove *T* wave disappears and becomes inverted in Leads I and II (Case 400*B*). On the other hand, Lead IV shows a persistently upwardly directed *T* wave, with a more pronounced slurring of the *Q–R–S* complexes. On the basis of the tracing in Case 400*C*, one would be justified in stating that only in Lead IV is there evidence of recent acute coronary occlusion, the routine 3 leads being negative. Thus it is shown by this serial electrocardiogram that an abnormal Lead IV can persist long after the disappearance of abnormal findings in routine 3 leads.

Summary and Conclusion. In 86 cases, Lead IV was studied in addition to the routine 3 leads, in both the anteroposterior and posteroanterior position.

A group of 25 normal cases shows a normal Lead IV to consist of a diphasic *Q–R–S* complex, with a definite deep *Q* wave. The *T* wave is inverted to the extent of 9 mm. and the normal Lead IV usually shows the *T* wave to be negative in the anteroposterior position; in 2 of our cases it was diphasic.

Deviation from a normal Lead IV consists in an absent *Q* wave, marked slurring of the *Q–R–S* complexes, absent or upwardly directed *T* waves.

A group of 40 cases of coronary artery disease with myocardial damage shows positive routine 3 leads in 28 cases (70 per cent); 12 show an abnormality in Lead IV and positive routine 3 leads (30 per cent); 3 (7.5 per cent) show abnormality only in Lead IV.

Four of 13 cases of acute coronary thrombosis (30 per cent) show an abnormal Lead IV, whereas the routine 3 leads are negative.

A serial study of a case of coronary thrombosis shows that abnormal Lead IV may persist long after abnormal changes have disappeared from routine 3 leads.

Since abnormal Lead IV proves positive in cases of coronary artery disease (7.5 per cent) and acute coronary thrombosis (30 per

cent), its employment as a routine electrocardiographic method both in private and hospital practice is advocated. The method carried out in this series was that of Wolferth and Wood, although in a few cases the posteroanterior position was also used and proved of value.

BIBLIOGRAPHY.

1. Wolferth, C. C., and Wood, F. C.: Am. J. Med. Sci., 1932, **178**, 30; Med. Clin. North America, 1932, **16**, 161.
2. Lieberson, A., and Liberson, F.: Ann. Int. Med., 1933, **6**, 1315.
3. Katz, L. N., and Kissin, M.: Am. Heart J., 1933, **8**, 595.
4. Hoffman, A. M., and Delong, E.: Arch. Int. Med., 1933, **51**, 947.
5. Goldbloom, A. A., and Kramer, M. L.: Med. Clin. North America, 1932, **15**, 1345.
6. Pardee, H. E. B.: Arch. Int. Med., 1920, **26**, 244.
7. Rothschild, M. A., Mann, H., and Oppenheimer, B. S.: Proc. Soc. Exp. Biol. and Med., 1926, **23**, 253.

ON THE USE OF HEAT, DESICCATION AND OXYGEN IN THE LOCAL TREATMENT OF ADVANCED PERIPHERAL VASCULAR DISEASE.

By Isaac Starr, Jr., M.D.,
HARTZELL PROFESSOR OF RESEARCH THERAPEUTICS, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(From the Medical Clinic of the University Hospital and the Laboratory of Pharmacology.)

The purpose of this paper* is to report the results of applying three therapeutic procedures, heat, desiccation and oxygen in the problem of treatment of advanced peripheral disease. Physiologic considerations and the experience gained point to their potential value. Gradually developing organic occlusion of a vessel is often compensated by the development of collateral circulation and by canalization of the occluded lumen. But, the circulation to an extremity may be diminished suddenly, as by thrombosis in a previously diseased main artery, and a critical period of acute ischemia results, accompanied by pain, indolent ulcers, or gangrene. This paper is concerned with such cases, and the aim of conservative treatment is to keep the part alive or to minimize the area of gangrene until collateral circulation is established.

Heat. When heat is applied by the usual heated cradle to the feet of a person afflicted with advanced peripheral vascular disease, pain may be relieved, but often it is intensified. Since these obser-

* Preliminary reports on certain phases of this work have appeared as follows: Starr, I., Jr.: A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, Proc. Soc. Exp. Biol. and Med., 1931, **29**, 166; On the Conservative Treatment of Gangrene of the Feet by a Selected Temperature, Oxygen and Desiccation, Trans. Assn. Am. Phys., 1932, **47**, 339. The first design of thermoregulated foot cradle was shown in the scientific exhibit of the American Medical Association, Philadelphia meeting, 1931.

vations were made when uncontrolled heat was applied, it seemed important to learn by experiment the range of temperatures in which the greatest degree of relief from pain is secured. Eleven patients with advanced peripheral vascular disease were chosen. All had gangrene; in only 1 (W. B.) was a pulse palpable in the vessels of the feet. In 6 of these, the diseased feet were placed in a water-bath at 25° C., and the temperature of this raised at the rate of 1° in 5 minutes. In 5, the presence of open lesions made prolonged immersion in water undesirable, and in these a similar experiment was performed by warming the air about the feet, the skin temperature being recorded by thermal junctions in 2 instances. The color of the skin was compared with those of Lewis' scale.[2] At temperatures under 30° C., the feet showed degrees of cyanosis, which varied in different locations, and the majority of the patients complained of pain. As the temperature rose, pain diminished or disappeared and the color of the feet improved, though it did not reach the normal in most locations. But at higher temperatures the feet usually became bluer and pain, if present before, returned. The optimum environmental temperature for relief of pain was found to be 33° to 35° C. (Table 1). This is approximately the same as that of the skin of normal feet when the vessels are fully dilated.[3]

TABLE 1.—PERIPHERAL VASCULAR DISEASE. DETERMINATION OF THE OPTIMUM TEMPERATURE.

Patient.	Diagnosis.	Kind of bath, water or air.	Temp. of freedom from pain, °C.	Temp. of best color, °C.
	I. Patients Suffering From Pain.			
C. W.	Diabetic gangrene of 1 toe	W	35 to 36	35 to 36
J. R.	Diabetic gangrene of 1 toe	W	32 to 35	33 to 34
M. A.	Diabetic gangrene of 1 toe	W	34 to 35	34 to 35
G. S.	Aortic thrombosis; endarteritis; gangrene of 2 toes	A	33 to 37	35 to 38
A. S.	Diabetic gangrene of 1 toe	A	27 to 35	31 to 34
C. G.	Diabetic gangrene of 1 toe	A	30 to 37	31 to 39
J. N.	Buerger's disease, gangrene of 1 toe; tip amputated	A	33 to 35	34 to 53
	II. Patients Without Pain (Sensation Impaired).			
A. S.	Diabetes; 2 toes infected	W	....	34.5 to 40
W. B.	Diabetes; 1 toe amputated, 3 infected	W	....	37.5 to 40
D. F.	Diabetes; intermittent claudication	W	....	22 to 38
F. T.	Diabetes; great toe amputated; unhealed	A	....	33.5 to 35.5

The changes in color with changing temperature may be interpreted according to well-known physiologic conceptions. Because of the reduced circulation, the patient's ability to maintain the tem-

perature of his feet against that of the environment is impaired. A cool environment reduces the tissue temperature and so causes vasoconstriction and blueness analogous to that seen in normal persons exposed to more severe cold. On the other hand, a hot environment raises the tissue temperature and so causes increased tissue metabolism and demand for oxygen. The increase in circulation which would normally follow is prevented by the vascular disease, so blueness again results.

TABLE 2.—PERIPHERAL VASCULAR DISEASE. EFFECT OF INCREASED OXYGEN CONCENTRATION.

Patient.	Diagnosis.	Oxygen, per cent.	Color.	Sensation.
H. K.	Rheumatic heart disease; embolism; gangrene of both legs	21	XI	Severe pain.
		80	V	Complete relief.
J. N.	Buerger's disease	21	X	Uncomfortable.
		80	VII	Partly relieved.
A. S.	Diabetic gangrene of great toe	21	XI	Severe pain.
		80	X	Went to sleep.
G. S.	Aortic thrombosis; endarteritis; gangrene of 2 toes	21	XV	Severe pain.
		84	VI	Sleeping.
A. S.	Diabetes; chronic ulcer	21	VIII	No pain.
		87	VII	No pain.
C. G.	Diabetes, gangrene of great toe	21	X	No pain.
		80	VIII	No pain.
W. B.	Diabetic gangrene; 1 toe amputated, 3 infected	21	XI	No pain.
		78	IX	No pain.
S. J.	Arteriosclerotic gangrene, with small patches on toe and heel	21	XII	No pain.
		90	X	No pain.
W. J.	Buerger's disease	21	XIII	No pain.
		89	XI	No pain.

The colors are recorded by the Roman numerals used in the Lewis scale.[2] The brilliant red of reactive hyperemia is recorded as V, the most intense cyanosis as XVI. Intermediate colors are numbered correspondingly. The color of normal skin over the knuckles is usually VII. The colors here recorded represent the maximum changes observed.

Oxygen, Locally Applied. It has been demonstrated that oxygen can penetrate the human skin.[4,5] We were also aware that E. D. Churchill had employed oxygen as a means of local treatment. In our experiments, the feet of 7 patients showing gangrene or other lesions were tested. The foot was placed in a jar equipped with a rubber cuff to make an air-tight joint about the leg. The temperature was kept constant while the oxygen concentration of the air within the jar was slowly raised. No change in color or sensation resulted from 50 per cent oxygen or lower. Concentrations above 80 per cent caused relief from pain and slowly developing change of color (Table 2). Some cyanotic areas became bright arterial red, others showed less change and in others the cyanosis persisted. The change was most marked when the feet were originally very blue. When originally red, as in the rubor of Buerger's disease,

the change was distinguishable with difficulty. In all these cases, the original color of the skin slowly returned when the oxygen in the jar was replaced by room air. No change in skin temperature accompanied the changes in color; hence the effect must have been due to penetration of oxygen into the blood and not to improved circulation. From the relief of pain which occurred, it would appear that lack of oxygen is one factor in the pain in gangrenous conditions.

Desiccation. When oxygen was applied locally, it was found necessary to prevent the undue accumulation of moisture within the gas-tight cover. It soon appeared that this desiccation alone was of distinct advantage in preventing the development of wet gangrene; it may also convert a wet into a dry gangrene and so prevent infection of the necrotic area.

Apparatus. The results of these experiments led us to design apparatus for the application of a controlled temperature, desiccation and oxygen to the feet of bed patients.

A Thermoregulated Foot Cradle. The ordinary foot cradle, somewhat enlarged, has been equipped with temperature-control apparatus and arranged so that air would circulate through it by convection (Fig. 1). An adjustable gas-filled mercury contact thermometer and relay were used at first. Later, less expensive bimetallic thermoregulators proved more durable, more easily regulated, but not quite as reliable. Their specifications are as follows: Differential, 2° C. or less; range, approximately 28° to 38° C. or over; to operate on 110-volt a.c. or d.c. lines without other resistance; to break a current of 3 ampéres without the use of a relay. A condenser, connected around the contact points, is desirable when direct current is used. Apparatus designed to regulate the temperature of water-baths, incubators, or to control the heating of houses will usually fill these requirements and may be obtained from many manufacturers. The list prices range from $8 to $15. In my experience, the more expensive types have had a more constant calibration and so have required less attention than the cheaper bimetallic thermoregulators.

The reliance on convection currents to circulate the air makes the temperature control far from perfect, and differences of from 2° to 3° C. may often be found in the air within the cradle. Larger differences occur if it is not well wrapped up with blankets. This degree of regulation seems good enough for clinical purposes, and mechanical stirring appears unnecessary.

For the Local Application of Oxygen to the Feet. Attempts to employ a simple method, as placing the foot within a rubber bag, failed because of the accumulation of moisture, the skin becoming macerated. So a smaller thermoregulated cradle (length, 24 inches; breadth, 17 inches; height, 12 inches) was surrounded by a sleeve-like cover of rubberized cloth, one end of which was bound firmly to the base of the cradle, the other bandaged loosely about the patient's thigh. A large celluloid window was inserted in this cover so that the foot and leg could be observed. The cradle design was modified from that of Fig. 1 in order to place all wiring and contacts outside the oxygen and so avoid the danger of fire.

When filled to a concentration of 50 to 80 per cent oxygen, the loss amounted to from 5 to 10 per cent an hour. Fresh oxygen was admitted 3 or 4 times a day, analyses being made before and after each addition. From 60 to 80 per cent oxygen was usually required to maintain the leg at its best color.

For Desiccation. Pans containing granular calcium chlorid were placed under the lights of the thermoregulated cradle. A shelf of copper gauze was placed above the lights (Fig. 1). On this, lumps of $CaCl_2$ were scattered, so that the warmed air on rising passed among them. By this means the relative humidity could be kept down to about 55 to 65 per cent in damp weather. In winter the artificial heating so reduces the humidity of the ward air that a much lower figure can be attained. Over 50 cc. of water has been collected in the desiccators daily in certain cases.

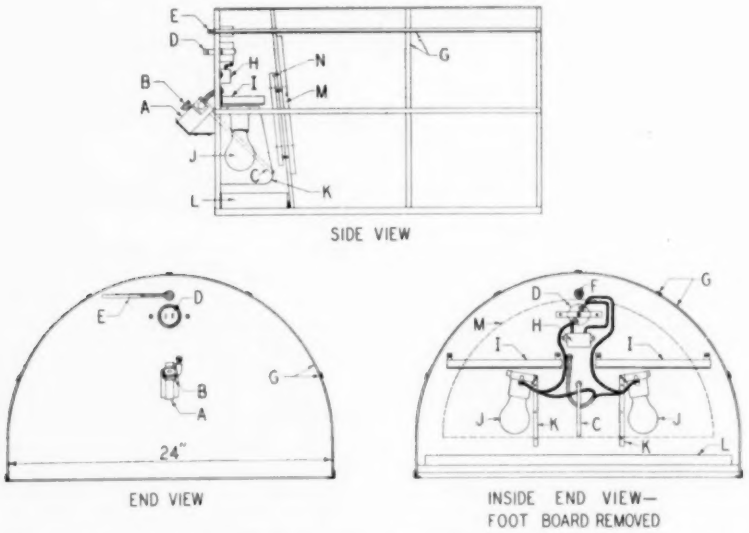


FIG. 1.—Thermoregulated foot cradle. Drawn to scale. Length, 2 feet; max. width, 2 feet; max. height, $1\frac{1}{4}$ feet. *A*, Thermostat; *B*, thermostat regulating knob; *C*, bimetallic thermostat element; *D*, male attachment plug (female attachment on cord); *E*, thermometer stem; *F*, thermometer bulb; *G*, cradle frame (main framework of round-edge iron strip $\frac{1}{2}$ by $\frac{5}{32}$ inch, other pieces $\frac{1}{4}$ by $\frac{1}{32}$ inch, joints welded); *H*, condenser for d.c. current (not used on a.c.); *I*, screen for $CaCl_2$, of copper gauze; *J*, lamp; *K*, lamp shield and support, of galvanized iron sheet; *L*, pan for $CaCl_2$; *M*, footboard, of $\frac{3}{4}$-inch 3-ply birch; *N*, cleat for footboard (it also shields footboard from direct light rays and possible overheating). When in use, the cradle is wrapped up in 3 or 4 layers of blankets; 15- or 25-watt lamps will usually give sufficient heat. The cradle shown is large enough to admit both feet and small enough to be easily transported in a passenger automobile. If the cradle is to remain in the hospital, it may be advantageously constructed with greater width so that it covers the entire foot of the bed.

Clinical Methods and Results. Thirty-five consecutive patients with advanced peripheral vascular disease have been treated in the medical wards. In all, there was a serious question whether amputation was not inevitable. The diagnoses and local findings have been given in Table 3, p. 505. The marked degree of impairment of circulation is further indicated by the fact that in only 2 cases (J. B. and W. B.) did the histamin puncture[1] on thedorsum of the foot cause a wheal or flare.

In addition to the three methods of treatment which were the particular subject of this study, the usual well-recognized procedures were employed. These included rest of the part, surgical treatment of open lesions and the careful management of diabetes when this was present. For this reason one must be particularly cautious in attributing results to any one or other of the means employed.

In most cases, the diseased foot was first placed in an ordinary foot cradle containing an electric bulb. After 24 to 48 hours, the thermoregulated cradle was substituted. If pain was not relieved within a few days, other procedures were tried in certain cases. These included the vasodilator drugs, acetyl-β-methylcholin or sodium nitrite, oxygen in a few cases and nerve block. Only when conservative measures failed was amputation performed.

When the *thermoregulated cradle* was used, the initial temperature was usually 34° C. When necessary for the maximum comfort of the patient, the temperature was changed. The foot was kept in the cradle continuously until the acute condition had subsided.

All the patients agreed that greater comfort was secured from the use of the thermoregulated cradle than from either the unregulated or the unheated type. In about $\frac{1}{2}$ the cases, relief was complete after a few days in the regulated heat. The cases not completely relieved fell largely into two definite groups: those with rapidly advancing gangrene and those with retained infection. The latter often had complete relief after the infection was drained. Therefore, very few of our cases required any sedative, only 2 required nerve block, and in none did severity of pain force amputation. This contrasts strongly with our previous experience in which the inability to control pain was so often the factor which drove the patient to accept amputation. Therefore, we have no doubt that the controlled heating relieves pain.

Our data on the effect of controlled heat on healing are also suggestive. In 2 cases of diabetes (W. B. and F. T.), toes had been amputated, but healing had not occurred under hospital treatment of 2 and 4 months respectively; it did occur slowly after the legs had been placed in a thermoregulated cradle. In several cases, indolent lesions began to heal when the cradle was applied, but in other cases no such stimulation of healing was observed. In 2 elderly patients, in whom gangrenous areas were removed below the line of demarcation (see below), contrary to expectation, healing of the stump occurred while the thermoregulated cradle was employed.

Application of 50 to 80% *oxygen*, together with regulated heat, has been tested in 4 cases only; in these the conditions were so severe that loss of both legs was threatened and operative risk excessive. All had advancing gangrene and suffered intense pain. In only 1 was there any suggestion that advance of the gangrene was delayed. There was, however, a change in color in every case, together with definite partial relief of pain. This was seen especially clearly in

1 instance in which the oxygen application was faulty. The pain became more severe when the oxygen leaked out and lessened whenever more oxygen was added. In the other cases, the effect on pain was indicated by the reduction in the dosage of sedative drugs which was possible during the use of oxygen.

Desiccation was used whenever frank gangrene was present. When open infections were present, it caused crusting and interference with drainage. In the first case treated, the gangrenous toe dried up and hardened except in the area of contact with the next toe. Here wet gangrene developed, at the only spot to which the dry air had no access. In the subsequent 14 cases, the toes being kept apart, the gangrenous areas become mummified and shrivelled to half their original size, the surface becoming as hard as a golf ball. Even though blebs formed, the moisture dried up so quickly that sloughing and infection did not follow. This will be illustrated in the cases given below.

In order to put these methods to more severe test, they were given a prolonged trial in certain cases in which high amputation is the accepted method of treatment but in which, because of complications, the operation involved unusual risk. These cases will be reported in detail together with one in which the results which followed the use of an unregulated cradle contrast strongly with those which followed the application of controlled heat.

Case Reports. CASE 1.—Mrs. H. K., aged 21, with rheumatic heart disease since childhood, became decompensated after Cesarean section. She improved for 6 weeks, but suddenly had an embolus into the right leg followed 3 days later by a similar catastrophe in the left leg.

On admission she showed the signs of a greatly enlarged heart, auricular fibrillation, mitral stenosis and pronounced aortic regurgitation. The legs were cold and edematous, with mottled cyanosis below mid-leg. No pulsation could be felt below the popliteal spaces. The pain in the legs was agonizing in spite of large doses of morphin.

Digitalis was continued in full doses throughout her illness.

The more painful leg (right) was put in the thermoregulated cradle, which was filled with oxygen and desiccated by calcium chlorid; the left was put into the usual cradle warmed by a single bulb. The right leg became a much better color, many areas turning bright red, and pain in it largely disappeared. She still suffered severely from the left leg. Two days later, the cradles were interchanged, with relief of pain and improvement in cyanosis of the leg within the regulated temperature and oxygen, but pain returned to the other leg. Two days later the apparatus was altered so that both legs could be placed within the regulated temperature and oxygen, and the relief was very great, morphin being needed only about once in 4 days.

Gangrene slowly ascended both legs at an equal rate, uninfluenced by the treatment employed. Blebs formed in the pregangrenous zone; they ruptured and the fluid dried up. The gangrenous areas shrivelled to about ½ the normal size of the part, and the surface became hard as a golf ball. From 40 to 50 cc. of water were collected by the desiccators each day at this stage. The line of demarcation eventually formed below both knees and the limb blackened, shrivelled and hardened up to that point. During the first month, the patient had no fever; the leukocytes, elevated on

TABLE 3.—SUMMARY OF CASE RECORDS.

Pulse | Limit of | Local treatment.

TABLE 3.—SUMMARY OF CASE RECORDS.

Date.	Patient.	Age, years.	Diagnosis.	Local lesion on admission.	Pulses.		Limit of dependent rubor or cyanosis.	Local treatment.			Relief of pain, if any, in 3 days or less.	Remarks.
					Dorsalis pedis.	Post. tibial.		Temp. ° C.	Oxygen.	Desiccation.		
Jan., 1931	C. W.	58	Diabetes	Ulcer of 1st toe	0	0	Ankle	34	—	—	Complete	Healed; leg well for 2 years.
Feb., 1933	C. W.	..	Diabetes	Ulcer of 1st toe	0	0	...	34	—	—	Complete	Healed.
Mar., 1931	E. A.	64	Diabetes	Gangrene spot on 1st toe	0	0	Ankle	34	—	—	Considerable	Healed slowly; leg well for 2 years, except for claudication.
Feb., 1931	J. R.	71	Diabetes	Infected 1st toe	0	0	½ dorsum	34	—	—	Almost complete	No healing; very weak; inoperable; died several months later.
Dec., 1931	A. S.	74	Diabetes	Ulcer of heel; paronychia, 1st toe	0	0	Ankle	34	—	—	Very little	Healed slowly; relapsed in 3 mos.
Mar., 1932	A. S.	..	Diabetes	Gangrene of 1st toe	0	0	...	34	+	+	Slight	Gangrene ascended steadily; amputation in 10 days.
July, 1931	F. T.	69	Diabetes	Unhealed amputation of toe	0	0	Toes	34	—	—	No pain	Healed slowly; well 1 year later.
Jan., 1932	W. B.	46	Diabetes	Gangrene, tip of 3d toe; unhealed amp. of 2d toe; infection of 1st and 4th toes of rt. foot	+	+	Toes	34	—	—	No pain	Healed slowly; well 18 mos. later. Case 4.
June, 1932	W. B.	..	Diabetes	3d degree burn, dorsum of left foot	+	+	...	34	—	—	No pain	Healed; well 1 year later.
April, 1932	C. G.	57	Diabetes; angina pectoris	Gangrene of 1st toe	0	0	Toes	34	—	+	Moderate	See Case 2.
May, 1932	M. B.	68	Diabetes	Gangrenous spot at base of 5th toe	±	0	Slight	34	—	—	Complete	Healed promptly; well 6 mos. later.
May, 1932	J. B.	44	Diabetes	Gangrenous spot on great toe	+	+	Ankle	33	—	—	Complete	Healed; well 1 year later.
Nov., 1932	H. S.	55	Diabetes	Gangrene of 3 toes	0	0	...	34	—	+	Slight	Amputation as soon as acidosis was controlled.
Dec., 1932	R. S.	60	Diabetes	Gangrene of 1st toe and dorsum	0	0	Ankle	34	—	+	None	Gangrene ascended rapidly; amputation after 3 days.
Dec., 1932	W. T.	65	Diabetes	Gangrene of 4th toe	0	0	Ankle	31	—	+	Slight	Gangrene ascended rapidly; amputation in 2 days.
Jan., 1933	L. G.	70	Diabetes	Gangrene of 1st and 2d toes and dorsum	0	0	Ankle	34	—	+	Slight	Gangrene ascended rapidly; amputation in 2 days.
Sept., 1932	C. B.	51	Diabetes	Blebs on each toe of right foot	0	0	...	33	—	+	Almost complete	Marked temporary improvement; reported return of trouble 3 mos. later; improved again.
Jan., 1932	W. J.	58	Thr. ang. obl.	Sup. gangrene of 1st toe and heel	0	0	Ankle	30	—	—	Complete	Healed quickly; no trouble for 10 months.
Dec., 1932	W. J.	59	Thr. ang. obl.	Ulceration of 1st toe	0	0	Ankle	30	—	—	Very slight	Toe became gangrenous; low amputation.
Feb., 1932	J. N.	26	Thr. ang. obl.	Unhealed amputations for gangrene of both 1st toes	0	0	Distal ½ dorsum	34	—	—	Complete	Healed in 1 month; well 1 year later.
Nov., 1932	H. C.	55	Thr. ang. obl.	Gangrene of 1st, 2d and 3d toes and adjacent dorsum	0	0	Ankle	30	—	+	Almost complete	Gangrene extended steadily; amputation after 10 days.
Mar., 1933	N. P.	37	Thr. ang. obl.	Gangrene of tip of 1st toe	0	0	Distal ½ dorsum	34	—	—	Complete	Lesion débrided; healed slowly; pain returned, then disappeared.
Dec., 1932	E. K.	50	Raynaud's disease; polycythemia vera	Gangrenous spot on 5th toe	+	+	Ankle	32	—	—	Complete	Healed in 1 month.
Nov., 1931	G. S.	42	Thrombosis, abdominal aorta	Gangrene of both feet	0	0	Ankle	36	+	+	Marked, but not complete	Legs amputated; died of gas bacillus infection; necropsy.
June, 1932	N. R.	23	Postpartum femoral thrombosis	Gangrene of right leg	0	0	Knee	34	+	+	Marked	Amputation when line of demarcation formed.
Jan., 1932	H. K.	21	Endocarditis; embolism of both legs	Gangrene of both legs	0	0	Knees	37	+	+	Great but not complete	See Case 1.
June, 1932	F. K.	74	Arteriosclerosis	Gangrene of 1st right toe	0	0	½ dorsum	34	—	+	Almost complete	See Case 3.
Dec., 1932	M. P.	72	Arteriosclerosis	Discolored painful 1st toe	0	0	Toes	34	—	—	Complete	Restored to normal; well 6 months later.

admission, had fallen to normal and remained there. There was little pain, though restlessness and discomfort necessitated small doses of morphin ($\frac{1}{6}$ grain) occasionally. Her general condition had improved.

The second month was characterized by deepening of the line of demarcation (Fig. 2) and the development of small areas of pyogenic infection in the exposed stumps. For the first time, the gas within the cradle became slightly foul. The abscesses ruptured and dried up and were succeeded by similar infections in other places. No fever nor leukocytosis was present at this stage, but the general condition became worse, edema of the buttocks became more marked, a bed sore formed and anemia increased. The serum proteins were found to be diminished (4.46 per cent). Ammonium chlorid and theocin were given without effect. Urea was followed by slight diuresis. The appetite was very poor, and restlessness rather than pain required the use of more morphin ($\frac{1}{6}$ grain) 2 or 3 times a day.

By the beginning of the 3d month, there was frank sloughing in the line of demarcation, the air within the cradle became very foul and a more active policy was decided upon. The cradle and oxygen were abandoned. The stumps were débrided, and a few days later the gangrenous area was amputated below the line of demarcation by Dr. L. K. Ferguson, and

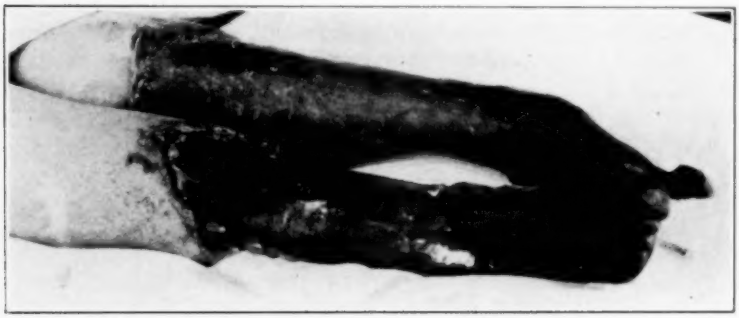


FIG. 2.—Legs of patient H. K., 6 weeks after the onset of gangrene.

maggots were applied to the stumps. These procedures caused no pain and required no anesthetic. They were followed by transient fever and leukocytosis which soon diminished. The stumps were quickly cleaned up by several applications of maggots and commenced to granulate nicely. But 2 weeks later, the patient's general condition became worse. Edema increased to the axillæ, she became jaundiced and numerous bed sores developed. She died 3 months and 6 days after her admission. The stumps were clean and granulating well when she died.

CASE 2.—C. G., aged 57, with diabetes which had been diagnosed 5 years before admission, developed attacks of angina pectoris 5 months before. These occurred after less and less exertion until he suffered from them in bed. Two months before admission, the left great toe became painful, then gangrenous. Amputation was repeatedly advised but refused. He consented to come to the hospital only when assured that no amputation would be performed.

On admission, both lower extremities were edematous. The first left toe was gangrenous to the first joint; the line of demarcation was infected. When dependent, rubor covered the toes and extended over the dorsum at the base of the gangrenous toe. Histamin reaction showed neither wheal nor flare on the left dorsum. No pulsation could be felt below the left femoral; the radial arteries did not pulsate and the thickening and

beading of the palpable vessels were extreme. Roentgen ray showed calcification in all vessels of the lower extremities.

The diabetes was easily controlled without insulin. The diseased foot was put in a cradle set for 34° C. This was followed by almost complete relief of pain, but he continued to have attacks of angina almost daily. A week after admission, the gangrenous area was trimmed off with scissors and maggots applied to the stump on two occasions. After this, the attacks of angina became far less frequent, the general condition improved and the stump gave every evidence of healing. The improvement lasted about 10 days. Then a few red streaks were seen in the leg and this was followed by high fever, leukocytosis and signs of consolidation in the chest. He died in a few days. Necropsy was not permitted. The stump appeared to be in excellent condition at time of death, but that it was the source of an infected pulmonary embolus seems not unlikely.

Case 3.—F. K., aged 74, had had angina pectoris for several years. For the last 6 months, the right foot had been cold, and swollen at night. Three weeks ago he noticed pain and tenderness in ball of the right first toe and found a draining sinus there. Soon a black spot appeared on the tip of this toe. It increased in size until it extended to the first joint. He was admitted, June 15, 1932.

Physical examination showed marked sclerosis of peripheral vessels. No pulsation could be felt below the popliteals. The tip of the toe was gangrenous and there was a draining sinus under the ball of the great toe. When hung down, redness extended to the ankle. The legs were thin and the skin shiny. Roentgen ray showed destructive osteomyelitis of terminal phalanx and first metatarsal of the gangrenous toe and gave evidence of sclerosis of the vessels of the foot.

The patient's foot was put in a cradle set at 34°, with $CaCl_2$. Pain, which had prevented sleep when the old type of cradle was applied, was relieved almost completely. Pain returned one night when the thermoregulated cradle was accidentally disconnected and was relieved when the connection was repaired. The gangrenous tip shrivelled and the line of demarcation did not advance. About 2 weeks later, the gangrenous area began to separate off and small infections developed in the fissure. These ruptured or were opened and dried up, but others kept developing. Two weeks later, redness and swelling began to extend to the dorsum. The gangrenous portion of the toe was then amputated by Dr. L. K. Ferguson below the line of demarcation without anesthesia. This proved to be more painful than had been expected. After this, all signs of extension of inflammation disappeared, though the foot became somewhat edematous. The stump did well, the anterior part closed in nicely, the healing of the lower part was held up by the sloughing tendon. Eventually maggots were applied to this area on 2 occasions. After this, the wound cleaned up nicely and healed slowly. Recovery was complicated by the appearance of a small abscess on the dorsum of the foot which was opened and drained, and eventually healed. For the last 6 months, the patient has been walking on his foot, his activity being limited only by his angina pectoris.

Case 4.—W. B., aged 46. Diabetes had been known for 3 months before admission. At this time, the right second toe became painful, then gangrenous. One month later, the toe was amputated at another hospital where he was given insulin and his foot placed in an unregulated cradle. The wound failed to heal and the adjacent toes became involved; so, 2 months after the amputation, he was sent to the University Hospital.

On admission, pus exuded from the ball of the right great toe, the tips of the 3d and 4th toes were dusky and wrinkled, and pus could be expressed from them. Pus could likewise be expressed from the site of amputation. The foot was much swollen. The dorsalis pedis pulse was palpable but the

posterior tibial pulse was absent. There was redness of the toes when the foot was dependent. The histamin reaction showed a normal wheal but no flare on the foot. Sensation to pin prick, heat and cold and vibration was greatly impaired on the foot; that to touch was normal except on the toes. When the hands were placed in hot water, no change in the temperature of the toes occurred, indicating a high grade of organic obstruction to blood flow.[6] Roentgen ray showed that the head of the second metatarsal was rarefied and irregular and the rest of the bones in the anterior part of the foot showed marked osteoporosis. He had no pain at any time, doubtless due to the advanced neuritis.

The foot was placed in a cradle set to give 34° C. Wet dressings were applied and the toes débrided. This left the bones exposed on the tips of the 3d and 4th toes. After the infected areas had been well opened, no dressings were applied. The infections subsided slowly and in 2 months healing was complete. He has had no trouble with this foot in the 18 months since his discharge and has been working most of this time.

Discussion and Summary. The considerations which should govern the therapeutic application of heat in peripheral vascular disease are not identical with those which obtain in conditions in which the blood supply is normal. If the vessels are inadequate to carry sufficient blood to meet the increased oxygen demands of heated tissues, positive damage may result from degrees of heat which would be beneficial, were the blood supply more nearly normal. It is well known that "baking" a foot with undiagnosed peripheral vascular disease may cause gangrene: I have seen 3 instances. The possibility of damage from more moderate overheating may well be greater than has been realized. In the conditions under discussion, the ordinary foot cradle, covered with blankets and heated by one or more electric lights, is to be condemned because of the likelihood of overheating which it provides. In many cases, it causes unnecessary pain. Our experience indicates that the optimum temperature in peripheral vascular disease is from 30° to 34° C.; it is the temperature at which the tissues are accustomed to function. The physiologic method of treatment is to maintain this temperature by artificial means when the ability to do so naturally has been lost. While it is possible to accomplish this with the ordinary foot cradle, if careful attention is given to it, this result is far more easily and certainly attained by such a thermoregulated cradle as has been described. Evidence of its greater effectiveness in relief of pain and in promoting healing has been set forth.

Experience with the application of oxygen, together with controlled heat, has been insufficient to justify its advocacy as a routine element in treatment of peripheral vascular disease at the present time. Its use has been limited to very severe cases in which its contribution to the relief of pain was the only definite result.

Desiccation of the air within the thermoregulated foot cradle caused rapid drying of exposed gangrenous areas. It is a safe inference that it will prevent infection of such areas. It did not prevent

infection from forming in the line of demarcation when the gangrenous part began to separate.

The limitations of our methods can be seen by reference to Table 3. When relief of discomfort and cessation of the advance of lesions did not soon follow their application, we quickly turned to more radical procedures. The only deaths in the series have been described (Cases 1 and 2; and G. S., Table 3). Two cases, after having a functional restoration of their feet for 3 and 11 months, relapsed and came to amputation. Two others have had lesions return after initial recovery; both of these again did well under conservative methods. On the other hand, in 5 cases in which competent surgeons deemed amputation inevitable, the patients regained functional use of their limbs and have maintained it during the period of observation.

Therefore, we believe that these methods will form a useful supplement to other well-recognized means of treatment and that they may secure the recovery of certain cases which would otherwise come to amputation. In more severe cases, they may permit the continuance of conservative measures over longer periods of time without too much discomfort or danger. This will lead to new problems, some of which are already before us. The eventual solution of these problems might save much of the functioning tissue now lost because amputation must be performed so far above the level of the lesion.

REFERENCES.

1. Starr, I., Jr.: Am. J. Med. Sci., 1930, **180**, 149.
2. Lewis, T.: Heart, 1929, **15**, 1.
3. Morton, J. J., and Scott, W. J. M.: J. Clin. Invest., 1930, **9**, 235.
4. Shaw, L. A., Messer, A. C., and Weiss, S.: Am. J. Physiol., 1929, **90**, 107.
5. Goldschmidt, S., and McGlone, B.: Proc. Soc. Exp. Biol. and Med., 1932, **29**, 827.
6. Gibbon, J. H., Jr., and Landis, E. M.: J. Clin. Invest., 1932, **11**, 1019.

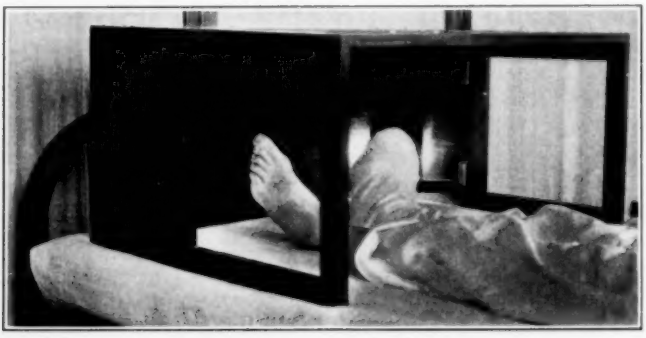
A CONSTANT TEMPERATURE FOOT CRADLE.

By Elmer L. Sevringhaus, M.D.,
Associate Professor of Medicine, University of Wisconsin, Madison, Wis.

Temperature control of the environment of the feet is desirable in cases of gangrene, thrombosis, ischemia from spasm or sclerosis, or of sepsis. The use of continuous warmth, combined with different types of dressings, is usually difficult because of the labor involved in frequent changes of hot-water bottles, and the danger of excessive heat from hot water or electric warm pads. Automatic and exact control is provided by a cradle described by Starr.[1,2] Personal communication with Dr. Starr led the author to build a cradle of

similar dimensions and design. This was so obviously helpful in improving the comfort and facilitating the healing of gangrenous lesions that further improvements were made. These have now been in use for a year with results that are gratifying to patients and to the medical staff members who have observed their use with diabetic gangrene, both dry and septic.

The original cradle of Starr was the conventional bed cradle of metal, covered with $\frac{3}{8}$ inch mesh wire, and heated by an incandescent lamp which was placed in the remote end, behind a baffle board, to direct circulation of warm air and prevent contact burns. It was found necessary to cover the baffle board with a soft pad since it became too warm. The cradle was found to be unduly confining when employed continuously. Therefore a larger chamber was constructed, with dimensions allowing it to enclose both legs and feet comfortably. This was constructed of wood, and in one



Controlled temperature cradle in use, but with bed covers removed. (Note the glow of the lamp behind the baffle, the moist dressing on the right foot, and the availability of the feet for inspection.)

model the walls were made of two layers of ply-wood separated by about $\frac{1}{2}$ inch air space to conserve heat. These chambers rest on the standard single hospital beds so that the covers are readily draped over them. Patients are more comfortable with them than with the covers resting on the feet. The temperature control adds further to the comfort of the patient.

Dr. Starr employed a thermostatic contact breaker and relay to control the lights. This is here substituted by a Cenco-DeKhotinsky Thermo-regulator, obtained from the Central Scientific Co., Catalogue No. 13732. This is mounted so that the bimetallic element is suspended inside the cradle at about the height of the toes, while the adjusting knob is countersunk in the footboard of the cradle for ready regulating of the temperature. A small baffle board, perforated, keeps the feet from contact with the thermo-regulator. In the two corners of the cradle at the foot end are suspended two incandescent lamps, wired in series with the thermo-

regulator, and supplied from a detachable connector in the outside of the footboard. The lamps are separated from the cradle space proper by baffles made up of two layers of ply-wood separated by an air space. The foot cannot touch any hot or rough object inadvertently. This precaution is of prime importance. Temperature is measured by a Tycos bath thermometer which is suspended horizontally from one of the bars which form the top of the cradle. In one model it has been found convenient to hang a small thermometer in the chamber with the thermoregulator.

For convenience in changing dressings and inspecting feet the side panels are closed for only the first 10 inches. Also consideration of ease of storage and of handling led to hinging the top and side panels, so that the cradle, when not in use, folds to the size of a long suitcase, with no projecting equipment. When in use the cradle is 25 inches long, 32 inches wide, and 15 inches high.

The thermoregulator is sensitive enough to maintain temperature constant to within 1° C. The bath thermometers have been found accurate to within 2° F. In practice the temperature is adjusted to 95° F. and varied from that to suit the comfort of the individual. After the thermoregulator has been set it seldom needs further adjustment. It is wise to note the temperature daily to make certain that no accidental change of setting has been caused.

Experience has convinced those who have used it that the cradle is a comfortable and perfectly safe device, which has markedly facilitated the healing of lesions in the feet of a number of diabetics. The use of moist dressings in this cradle becomes at once the employment of continuous warm moisture with a minimum of nursing labor and no danger. The dressings are wrapped in oiled silk to reduce evaporation. When no dressings are employed the chamber is not warm enough to cause any uncomfortable dryness, although it is wise to use lanolin or cold cream on the skin. Current consumption is small. Two 40-watt bulbs are usually sufficient to maintain the temperature, when the bedclothing completely covers the cradle.

Since the preparation of this paper Dr. Starr has graciously submitted a copy of his most recent report on the use of heat, desiccation, and oxygen (preceding article). Our results agree very well with his, although no special efforts have been made to secure desiccation or to use oxygen. The larger air space may be responsible for the fact that we also have seen moist lesions drying without infection. Further protocols would add nothing but confirmation of the success Dr. Starr has described.

The author is indebted to Mr. J. R. Amacker, Stanley, Wisconsin, for many of the improvements in the design and convenience of this device. He is prepared to build these cradles to order, completely equipped.

REFERENCES.

1. Starr, I., Jr.: Proc. Soc. Exp. Biol. and Med., 1931, **29**, 166.
2. Starr, I., Jr.: Trans. Assn. Am. Phys., 1932, **47**, 339.

THE TREATMENT OF PELLAGRA WITH CERTAIN PREPARATIONS OF LIVER.*

By Julian M. Ruffin, M.D.,
ASSISTANT PROFESSOR OF MEDICINE,

AND

David T. Smith, M.D.,
PROFESSOR OF BACTERIOLOGY AND ASSOCIATE PROFESSOR OF MEDICINE,
IN THE DUKE UNIVERSITY SCHOOL OF MEDICINE,
DURHAM, N. C.

Many observers have noted that there is a close similarity in the symptoms of pellagra and pernicious anemia of the Addisonian type. However, the skin lesions in the one and the characteristic blood picture in the other serve to differentiate them.

Goldberger and Sebrell[1] have shown that daily doses of Liver Extract No. 343 (N.N.R.) by mouth will prevent and cure black tongue in dogs, a disease believed by some to be the analogue of pellagra. Liver and various extracts of liver, therefore, may be suitable agents for a more accurate analysis of the deficiency which brings about pellagra. Our purpose is to record preliminary observations on the effect of an oral and an intramuscular extract of liver in the treatment of pellagra.

Method. If not too far advanced, pellagrins usually recover when brought into a hospital and given a well-rounded diet. To study the effect of the liver preparations it was necessary to prepare a standardized diet similar to that upon which the patient developed the disease. In reviewing the foods consumed by our patients prior to their development of pellagra we were impressed with the similarity between their diets and the diet which Golderger and Wheeler[2] used in producing pellagra in convicts in Mississippi (Table 1). In addition to the vitamin G (or B_2) deficiency, Goldberger's original diet was lacking in vitamins A, C and D, and in iron, calcium, phosphorus, and complete proteins. A 2900-calorie diet† was prepared consisting of fat meat, field peas, rice, hominy grits, cane syrup, brown gravy, and lard. To supplement the vitamin,‡ mineral and protein deficiencies already mentioned, the patient received daily 90 cc. of cod liver oil, 45 cc. of tomato juice, 6 gm. of calcium gluconate, 6 gm. of iron and ammonium citrate, and

Table 1.—Goldberger Diet.

* Presented before the Medical Section of the North Carolina State Medical Society on April 18, 1933, and before the American Society of Clinical Investigation on May 8, 1933.

† We are indebted to Dr. W. A. Perlzweig of the Department of Biochemistry and to Mrs. J. H. Martin of the Department of Dietetics for their coöperation in preparing this diet.

‡ We wish to thank Mrs. Susan G. Smith of the Department of Physiology for her assistance in planning the vitamin supplement.

TABLE 1.—GOLDBERGER DIET.

Article.	Quantity (g.)	Protein (g.)	Fat (g.)	Carbohydrate (g.)	Minerals (in grams).								Calories.
					Ca.	Mg.	K.	Na.	P.	Cl.	S.	Fe.	
Corn meal	229.4	21.10	4.36	172.97	0.041	0.193	0.489	0.089	0.436	0.335	0.255	0.0021	
Grits	29.2	2.74	0.20	22.95	0.003	0.107	0.051	0.006	0.042	0.013	0.040	0.0003	
Corn starch	34.5	0.00	0.00	31.05									
Wheat flour	137.2	14.82	1.51	102.63	0.027	0.025	0.158	0.082	0.126	0.102	0.243	0.0014	
Rice	23.3	1.86	0.07	18.41	0.002	0.008	0.016	0.006	0.022	0.013	0.027	0.0002	
Cane syrup	34.3	0.16	0.00	25.93									
Cane sugar	58.3	0.00	0.00	58.30									
Sweet potatoes	92.3	1.66	0.65	24.39	0.018	0.026	0.366	0.036	0.042	0.087	0.022	0.0005	
Turnip greens	21.4	0.90	0.13	1.35	0.074	0.006	0.066	0.018	0.010	0.036	0.015	0.0004	
Cabbage	8.7	0.14	0.03	0.49	0.004	0.001	0.021	0.002	0.003	0.002	0.006	0.0001	
Collards	12.9	0.58	0.77	0.81	0.014	0.004	0.066	0.003	0.013	0.009	0.022	0.0002	
Pork fat	107.0	0.10	106.74	0.00									
Total	789.0	44.00	114.00	459.00	0.180	0.280	1.230	0.240	0.690	0.600	0.630	0.0050	3125

TABLE 2.—STANDARD BASIC DIET NO. 1.

Article.	Quantity (g.)	Protein (g.)	Fat (g.)	Carbohydrate (g.)	Minerals (grams).			Vitamins.					Calories.
					Ca.	P.	Fe.	A.	B.	C.	D.	G.	
Corn meal	92	8.3	2.0	69.0	0.011	0.1225	0.0006	.....	*	.....	.....	*	
Cane syrup	105	....	.....	89.2	.....	.....	.....	.....	+	.....	.....	+	
Flour	111	12.5	1.2	83.4	0.022	0.1030	0.0010	.....	+	.....	.....	−	
Lard	81	....	81.0										
Rice	25	2.0	0.1	19.6	0.0023	0.0240	0.0002						
Field peas	90	19.2	1.4	54.6	0.0756	0.0760	0.0052	+	++	.....	.....	+	
Hominy grits	51	4.3	0.3	40.6	0.0056	0.0734	0.0005	+	++	.....	.....	+	
Fat salt pork	60	1.1	51.3	0.0	0.0011	0.0115	0.0001						2890.0
Cod-liver oil	90 c.c.	....	90.0	.....	.....	0.0117	.....	++++	.....	.....	++++	++	810.0
Tomato juice	45 c.c.	0.4	0.1	2.0	0.005	.....	0.0002	++	++	++++	.....	++	10.3
Iron ammonium citrate	6	....	.....	.....	.....	.....	1.02						
Calcium gluconate	6	....	.....	.....	0.5580								
Cheese	60	17.4	21.6	.....	0.5586	0.4098	0.0007	++	++	.....	.....	....	264.0
Total		65.2	249.0	358.40	1.2392	0.8319	1.0285	++++	+++	++++	++++	+	3974.3

60 gm. of cheese, given as medication on the wards. This diet was called Standard Basic Diet No. 1, being deficient only in vitamin G (or B_2) (Table 2).

In this study, observations were confined to typical cases of pellagra with skin lesions, sore tongue, and gastro-intestinal disturbances. A total of 37 patients have been studied in detail, 23 of whom were given the Standard Basic Diet, and the remaining 14 given house diets as controls.

Effect of Sunlight on Pellagra. A marked improvement of the skin lesions occurred in 3 patients in the hospital on the Standard Basic Diet. A similar observation was made by Spies in 5 cases.[3] At the suggestion of Dr. H. L. Amoss these patients were exposed to direct sunlight to determine whether the disappearance of the lesions was due to the cure of the pellagra or to the protection from the sun afforded by the hospital. Three patients, receiving the Standard Basic Diet whose skin lesions had disappeared, were exposed to direct sunlight and developed the characteristic skin rash over the exposed areas.

Case Reports. CASE 1. (No. 5115).—R. S., a white male, aged 8, was admitted to the hospital May 1, 1931, with typical pellagrous lesions of the mouth, face, and hands. Beginning May 1, he was given the Standard Basic Diet No. 1, shown in Table 2. The lesions on the face and hands cleared rapidly during the following 6 days and by May 7 had practically disappeared.

Beginning May 7, the hands and feet were exposed to the direct rays of the sun for ½ hr. daily with the face protected by a wide brim hat. After 4 days of exposure, the face remained clear but the hands and feet were covered with new lesions. With the appearance of the skin lesions, the tongue and buccal mucosa became fiery red, and the patient had several large, liquid stools. On May 12, the exposure was discontinued and the patient was confined to the hospital. The Basic Diet was continued without the addition of any pellagra-curative factor and again by May 27, 15 days later, the lesions had disappeared and the tongue was normal. At this time, the hands were reëxposed to sunlight ½ hr. daily for 5 days, and the lesions returned.

On June 2, the Basic Diet was discontinued and he was given a house diet which contained an abundance of pellagra-curative substances. The skin lesions disappeared, appetite improved, he became alert mentally, and was discharged as well on June 13.

CASE 2 (No. 13406).—A. R., a white female, aged 25, was admitted to the hospital on April 21, 1932, with diarrhea, nausea, vomiting, nervousness, sore tongue, and dermatitis of hands (Fig. 1). There was a mild secondary anemia, but gastric analysis showed normal acidity after histamin.

She was given the Standard Basic Diet No. 1 and the right hand and arm were exposed to direct sunlight for 30 min., the rest of the body being carefully protected. This exposure was repeated the next day for 60 min. A violent reaction with vesiculation resulted, and at the elbow a second-degree burn (Fig. 2). The rash on the arm which had been protected from the sun had almost disappeared during this interval. At the same time her general condition became very much worse; anorexia was marked; the diarrhea had increased to 18 stools per day; and the tongue became much more painful. The arm of a control patient exposed for a similar length of time showed only a mild erythema.

A commercial wheat germ flour (150 gm.) including some bran (Wheatone) was added to the diet daily. Although the lesion on the arm improved slowly, her condition remained the same or worse. On May 6, 10 days

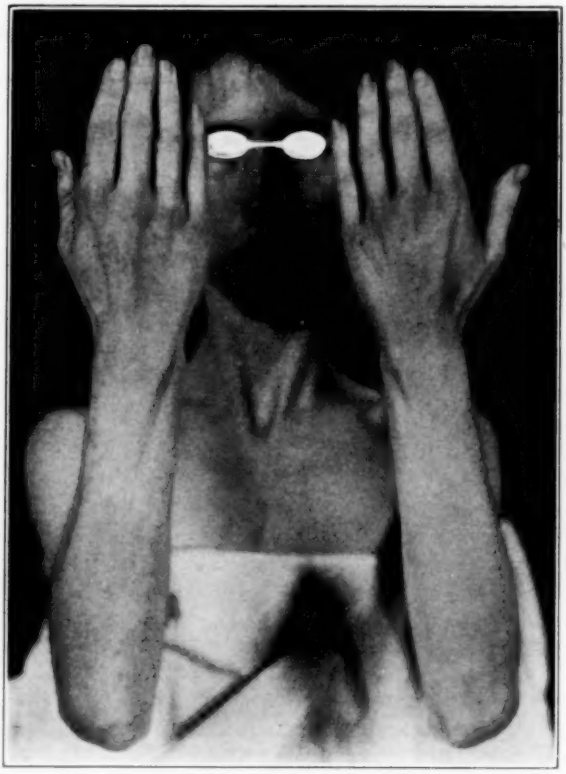


FIG. 1.—Case 2. Photographs of patient on admission to hospital showing slight dermatitis on hands and arms.

FIG. 2.—Case 2. Photograph showing extensive dermatitis on right hand and arm following exposure to sunshine.

after the last exposure to the sun, she was given a house diet and 90 cc. daily of an aqueous extract of liver by mouth. After 5 or 6 days a striking change was noted; the diarrhea had ceased; the tongue was no longer sore; the appetite improved; she began to gain in weight; and the skin lesions disappeared. She gained 5.5 kg. during the next 3 weeks. Beginning May 23, the right hand and arm were again exposed to the sun for 5 days, as before, and this time only a mild erythema, such as seen in a normal control, was observed (Fig. 3).

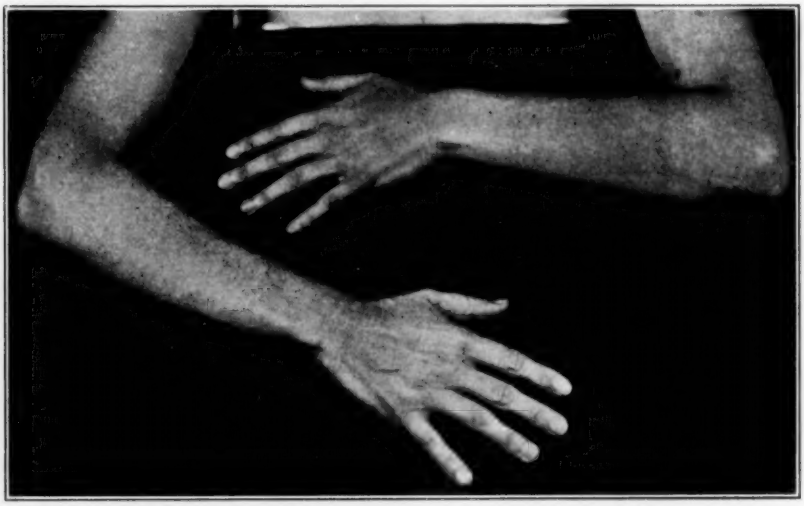


FIG. 3.—Case 2. Photograph showing absence of dermatitis following exposure to sunlight subsequent to administration of pellagra-curative substances.

Cases 1 and 2 illustrate the development of the characteristic skin lesions following exposure to sunlight, while subsisting upon Standard Basic Diet No. 1. Case 2 demonstrates that a unilateral dermatitis may be produced in pellagra by a unilateral exposure to sunlight. In Case 2 and in 9 other cases of pellagra the skin lesions did not recur after exposure to the direct rays of the sun, subsequent to the administration of pellagra-preventive substances.

Effect of Oral Administration of An Aqueous Extract of Liver. Ten patients with pellagra were fed the Standard Basic Diet for varying periods without improvement, and were then given 90 cc. of an aqueous extract of liver* by mouth daily. Without exception a striking clinical improvement began between the 3d and 5th days, and continued until complete recovery.

CASE 3 (No. 16778).—R. H., a white man, aged 66, was admitted to the hospital on July 29, 1932, with pellagrous lesions of the mouth, hands, arms and feet. He had a severe diarrhea and the feet presented marked secondary infection.

* This extract, known as Valentine's Liver Extract E-29 was furnished through the courtesy of the Valentine Meat Juice Company. In this paper it will be referred to as "an aqueous extract of liver."

He was given the Standard Basic Diet No. 1 for several days with little change in his condition and then, following exposure to the sun, 30 min. a day for 2 days, he became rapidly worse with anorexia, increased diarrhea, and nausea and vomiting. Starting on August 1, he was given 90 cc. of an aqueous extract of liver by mouth daily. Five days later he began to improve and by the 10th day the diarrhea had subsided, the tongue was normal, the nausea and vomiting had stopped, and the dermatitis had almost disappeared. After 3 weeks of this treatment he had gained 6 kg. and was feeling entirely well (Chart I).

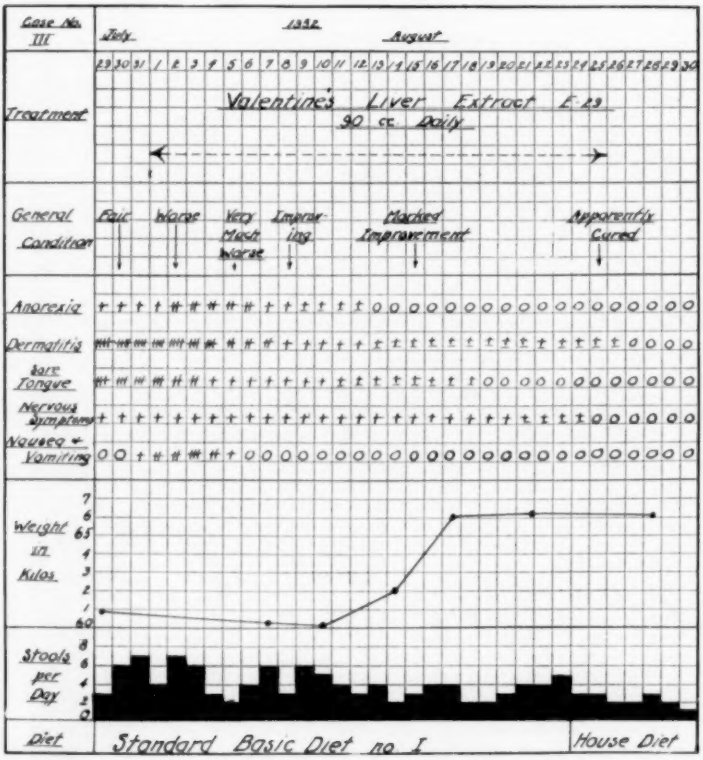


CHART I.—Chart from Case 3, showing symptomatology and result of treatment with an aqueous extract of liver, administered orally.

Effect of Oral Administration of a Powdered Extract of Liver. CASE 4 (No. 5114).—A. S., a white female, aged 26, was admitted to the hospital on May 1, 1931, with pellagrous lesions of mouth, hands, feet, and vulva.

Beginning May 1, she was given the Standard Basic Diet No. 1 supplemented by 3 vials of a powdered Liver Extract* by mouth daily. (Each vial contained the extract derived from 100 gm. of fresh liver.) Improvement was noted in the lesions on the hands and feet 4 days after the treatment was started. By May 22, the oral and buccal lesions were healed and the dermatitis had completely disappeared from the hands, feet, and vulva.

* Parke, Davis & Co.

Beginning May 22, one hand and arm were exposed to the direct sunlight for 15 min. each day and increasing to 1 hr. daily. After 7 days of exposure a normal healthy tan developed over the exposed area without evidence of dermatitis. The patient gained 3 kg. and was discharged in excellent condition on June 7.

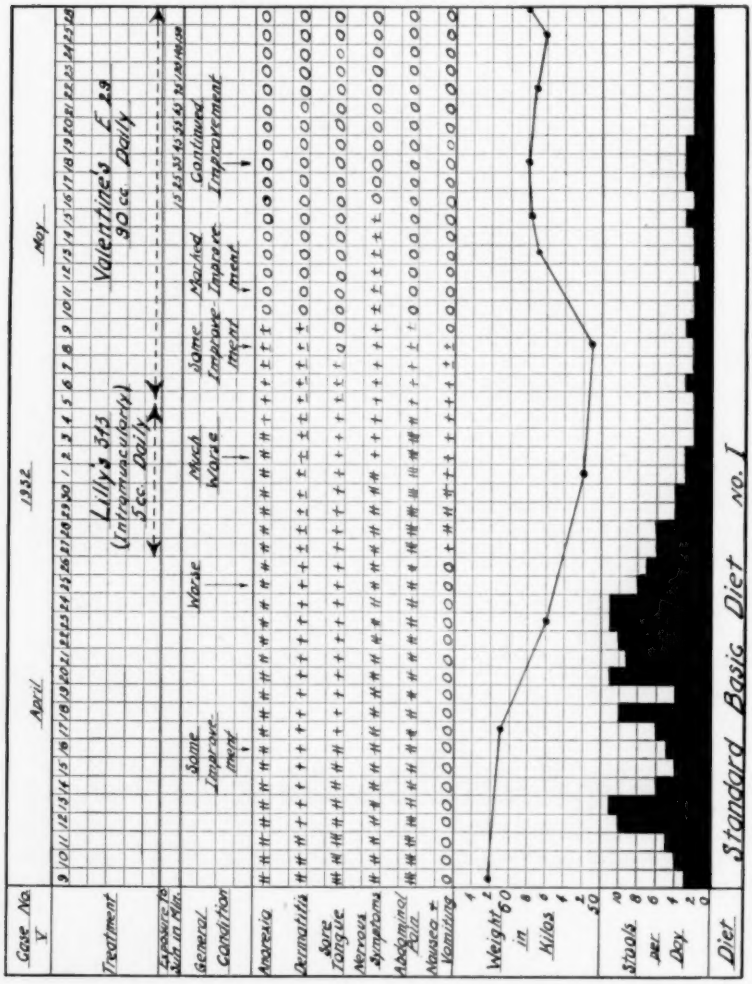


CHART II.—Chart from Case 5, showing symptomatology and result of treatment with liver extract, administered intramuscularly and orally.

Effect of Intramuscular Extract of Liver on Pellagra. Having obtained satisfactory evidence of the efficacy of an aqueous extract of liver in the cure of pellagra in 10 cases, and of a powdered extract of liver in 1 case, Liver Extract No. 343 (N.N.R.) was given intramuscularly to another series of patients.

CASE 5 (No. 13011).—T. I., a colored male, aged 49, was admitted to the hospital April 9, 1932, with the complaint of weakness, abdominal pain, diarrhea, sore mouth and rectum, and dermatitis of the hands.

Beginning April 9, the patient was given the Standard Basic Diet No. 1. The symptoms continued and the stools increased from 3 on April 9 to 11 on April 13, and then decreased to 5 on April 16, when he reported that he felt somewhat improved. The stools again increased to 11 per day by April 24, and all the other symptoms became aggravated. On April 25, he received two intravenous injections of calcium gluconate (10 cc. of 10% solution) and one injection on the following day. For 1 week, starting April 27, he received daily intramuscular injections of 5 cc. of Liver Extract No. 343. During this period his stools decreased, but all the other symptoms were aggravated and he developed nausea and vomiting so that this therapy was discontinued.

Beginning on May 6, he received 30 cc. of an aqueous extract of liver by mouth 3 times daily. Between the 3d and 6th day of the treatment the nausea and vomiting, abdominal pain, diarrhea, sore tongue, anorexia and dermatitis disappeared and he began to gain weight for the first time since admission. Exposure to direct sunlight for 4 days failed to produce skin lesions and he was discharged in good condition on May 29, 1932 (Chart II).

CASE 6 (No. 11803).—J. W., a white male, aged 21, was admitted to the hospital on May 9, 1932, with sore mouth, diarrhea, and dermatitis of hands and arms. The pellagra was complicated by a bilateral basal bronchiectasis and achlorhydria after histamin.

He was given the Standard Basic Diet No. 1 and 150 gm. of a commercial wheat germ (Wheatone) daily. The skin rash gradually subsided though his general condition became progressively worse with increased diarrhea, sore tongue, anorexia, and after 2 weeks, nausea and vomiting.

Beginning May 27, he was given daily 5 cc. of Liver Extract No. 343 intramuscularly. Very slight, if any, improvement was noted. The nausea, vomiting, diarrhea, and anorexia continued unabated. On June 3, 60 cc. of an aqueous extract of liver were given by mouth for 4 days and then increased to 90 cc. daily. Four days after instituting this therapy, the appetite improved rapidly; there was no further nausea and vomiting, and the tongue began to heal. The diarrhea subsided 8 days after starting this treatment. Beginning June 12, the right hand and arm were exposed to sunlight for 30, 40, 50 and 60 min. on successive days without recurrence of the skin rash. He gained weight rapidly and was discharged with no evidence of pellagra on July 11.

In these 2 cases and in 2 others treated in the same manner, little if any clinical improvement was observed during the period of intramuscular treatment with Liver Extract No. 343 in 5-cc. doses. These 4 patients promptly recovered when given 90 cc. of an aqueous extract of liver daily by mouth.

A 5th patient, who had shown no evidence of improvement with the intramuscular Liver Extract No. 343 in doses of 5 cc. daily, made a dramatic recovery after taking by mouth daily doses of the residue obtained from the alcoholic precipitation of 90 cc. of an aqueous extract of liver.*

* The addition of 95% alcohol to an aqueous extract of liver produces a precipitate which can be dissolved in water and given by mouth. This material was prepared for us by the Valentine Meat Juice Company.

Discussion. In order to determine the value of certain extracts of liver in the treatment of pellagra, a diet was prepared, similar to that which the patient had been taking prior to the development of symptoms. This Standard Basic Diet described above contains adequate amounts of proteins, fats, and carbohydrates, minerals and all the known vitamins except vitamin G (B_2). Patients with pellagra reported in this series did not improve on this diet, and 3 out of 4 dogs partaking of this diet died of typical black tongue between the 25th and 45th day of the experiment.

It would seem that the disappearance of the skin lesion does not necessarily indicate a cure of the disease since the lesions can be reproduced by exposure to direct sunlight, unless the patient has been protected by some pellagra-curative substances. The failure of the patient to develop skin lesions after adequate exposure to sunlight furnishes an additional clinical test of the cure of the disease.

The evidence presented here indicates that the bilateral symmetry of the lesion is due to bilateral exposure to sunlight. In this series it has been shown that unilateral lesions can be produced by unilateral exposure (Figs. 1, 2, and 3).

Oral administration of an aqueous extract of liver in doses of 90 cc. daily effected a cure in 10 cases; a powdered extract of liver in doses of 3 vials daily in 1 case; and an insoluble residue derived from the alcoholic extraction of an aqueous extract of liver in 1 case.

Of the 14 patients given house diets as controls, 3 were far advanced cases and died even though they received an abundance of known pellagra-curative substances. The remaining 11 patients recovered, their clinical course being about the same as that group of patients receiving the Standard Basic Diet and the aqueous liver extract by mouth.

Ramsdell and Magness[4] have reported the recovery of 22 cases of pellagra treated with 2 cc. daily of Liver Extract No. 343 intramuscularly. Their patients received a general house diet, which undoubtedly contained a considerable amount of pellagra-curative substances. In the present series of 5 cases treated with Liver Extract No. 343 intramuscularly in doses of 5 cc. daily, there was little or no clinical improvement. This discrepancy is explained by the difference in the diets, since our basic diet contained practically no Vitamin G (B_2).

It is of interest to note that yeast which cures pellagra[5] and black tongue in dogs[6] is ineffective in the treatment of pernicious anemia,[7] until it has been digested with normal gastric juice.[8] Since Spies[9] has shown that meat digested with the gastric juice of pellagrins with alcholhydria is effective in the treatment of pernicious anemia, it is probable that the deficiency in pellagra is entirely different from that in pernicious anemia.

Summary. 1. A diet has been prepared for the clinical study of pellagra which is adequate in all known nutritional elements except Vitamin G (B_2).

2. Exposure to direct sunlight in North Carolina in the spring and summer months produces dermatitis in active and potentially active pellagrins, but not in normal controls or in pellagrins who have received adequate treatment.

3. Ten patients with active pellagra, subsisting upon a basic diet deficient in vitamin G (B_2) showed satisfactory remission after the oral administration of 90 cc. daily of an aqueous extract of liver.

4. Five patients on the same basic diet showed little or no improvement when given Liver Extract No. 343 intramuscularly in doses of 5 cc. daily. When the oral aqueous extract of liver was substituted for the intramuscular extract, a dramatic clinical improvement began between the 3d and 5th days and continued until the patients were apparently well.

REFERENCES.

1. Goldberger, J., and Sebrell, W. H.: Public Health Reps., 1930, **45**, 3064.
2. Goldberger, J., and Wheeler, G. A.: Hygienic Lab. Bull. 120, February, 1920.
3. Spies, T. D.: Am. J. Med. Sci., 1932, **184**, 837.
4. Ramsdell, R. L., and Magness, W. H.: Ibid., 1933, **185**, 568.
5. Goldberger, J., and Tanner, W. F.: Public Health Reps., 1925, **40**, 54.
6. Goldberger, J., Wheeler, G. A., Lillie, R. D., and Rogers, L. M.: Ibid., 1928, **43**, 657.
7. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: J. Biol. Chem., 1928, **77**, 325.
8. Strauss, M. B., and Castle, W. B.: New Eng. J. Med., 1932, **207**, 55.
9. Spies, T. D., Payne, W., and Blakenhorn, M. A.: J. Am. Med. Assn., 1933, **100**, 144.

NEGATIVE RESULTS IN THE TREATMENT OF SICKLE-CELL ANEMIA.

By L. W. Diggs, M.D.,
Assistant Professor of Pathology, University of Tennessee, Memphis, Tenn.

(From the Departments of Clinical Pathology, Medicine and Pediatrics.)

It is generally conceded that the treatment of sickle-cell anemia is unsatisfactory. A review of the literature, however, reveals that the evidence upon which to base a fair appraisal of treatment results is scant, and that there is difference of opinion as to the effectiveness of certain forms of therapy.

Sydenstricker,[1] Yater and Mollari,[2] Leivy and Schnabel,[3] and Anderson and Ware[4] failed to observe benefit in patients with severe sickle-cell anemia following the use of liver or liver extracts. "Marked improvement on liver therapy" was reported by Levy[5] in 3 patients with "active" sickle-cell anemia, but the diagnosis is open to question in 1 of his cases, and in the others the anemia was mild. Brandau[6] added fresh spleen to his patient's diet for 25 days, without improvement. Iron, arsenic, calcium, iodids, alkalies and

general supportive measures have been used without apparent benefit. Transfusion has proved to be of aid in relieving the acute symptoms, but its effect has been temporary. Torrance and Schnabel[7] observed prompt relief of pain following the use of potassium thiocyanate in combination with potassium citrate and bicarbonate of soda, but this like other symptomatic treatments that have been tried, did not alter the anemia or prevent the recurrence of symptoms. Splenectomy as a therapeutic measure has been recorded in nine instances. Accurate evaluation of the procedure is difficult at the present time because of the inadequacy of the observations and controls. Permanent improvement in the anemia or in the clinical picture following the removal of large spleens in childhood remains to be proved. The removal of atrophic spleens characteristic of the later stages of the disease is useless and may be impossible.[8]

Because the number of therapeutic experiments under controlled conditions has been few, treatment observations made on 7 patients with sickle-cell anemia are here recorded. All were negro patients at the Memphis General Hospital and all had in common jaundice of a hemolytic type, anemia with marked regenerative signs, sickled erythrocytes, leukocytosis, fever, enlarged heart with hemic murmur, palpable liver and non-palpable spleen. Six of the cases were of the chronic type, and gave a history of constitutional inferiority from birth, and of recurrent attacks of sickness characterized by weakness, fever and varied symptoms, of which headaches, vomiting, and pains in abdomen, bones or joints were outstanding. The 7th case was a child with the sickle-cell trait, observed during what was evidently her first anemic episode. For the sake of brevity, the details of the clinical record are omitted in this paper, and the reports limited to the therapy used, and the alterations in the blood picture that followed.

Treatment Records. CASE 1.—A. M. C., female, aged 18, has been jaundiced and anemic since infancy. During 4 years the erythrocyte counts have varied between 2,000,000 and 3,000,000, the hemoglobin between 6 and 9 gm., the reticulocytes between 10 and 20 per cent (Fig. 1). The anemia was of the microcytic, hyperchromic, regenerative type. Typical sickled cells were always in evidence in the stained smears. Leukocytosis and thrombocytosis were constant. Free hydrochloric acid was found in small quantities in the gastric juice.

On the first hospital admission at 14, pills of ferrous carbonate, 1 gm., q. d., liver diet, and sodium cacodylate, 7.5 gr. every other day were given for 2 weeks. Clinically there was improvement, but the blood picture did not significantly change.

One year later, a 3-year-period of observation was started, during which time various antianemic measures were in succession tried, with control periods between the treatment experiments. The patient was a particularly favorable subject for investigation, for the anemia was marked, there were no evident complications and the patient faithfully reported week after week for blood studies. Except for short periods of debility, she was able to walk about a mile to and from the laboratory and do part-time work as a

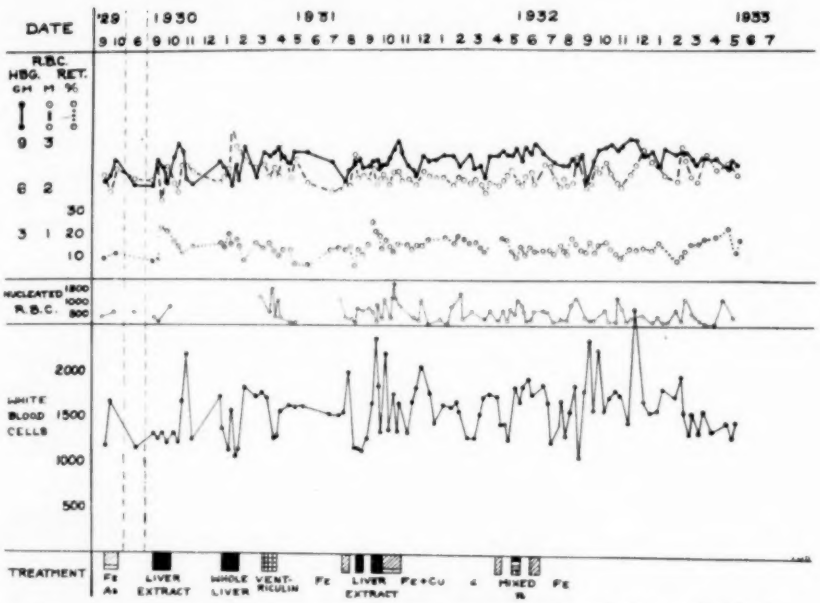


FIG. 1.—Case 1 (A. M. C.). Chart showing erythrocyte, hemoglobin, reticulocyte, nucleated red blood cell, and leukocyte values in relation to therapy.

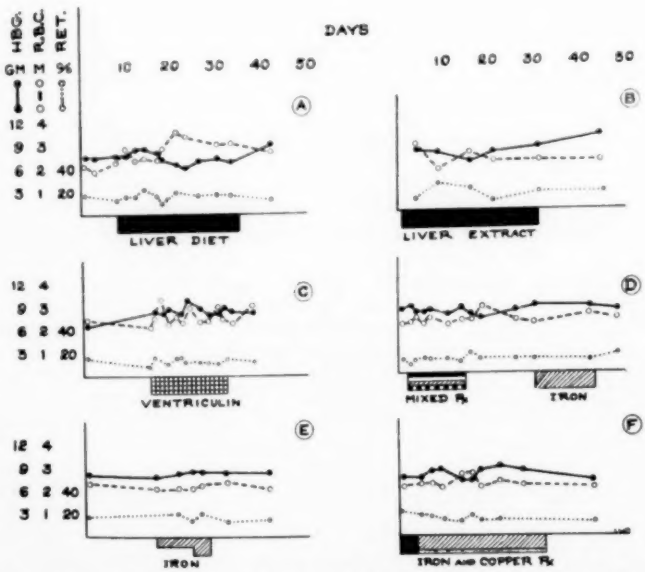


FIG. 2.—Case 1 (A. M. C.). Chart showing in more detail than in Fig. 1, the response of erythrocytes, hemoglobin and reticulocytes to various antianemic measures.

maid. There was reasonable evidence to assume that the patient honestly coöperated in taking the prescribed medicine, but when the less palpable drugs were used this was insured by administering the medication in the office.

The antianemic measures used and the dosages are as follows:

September, 1930. Liver extract,x, 60 cc., q. d. for 30 days (Fig. 2-B).

January, 1931. Whole liver, 300 gm., q. d. for 27 days (Fig. 2-A). (The patient was in the hospital for this experiment, and under careful dietary supervision).

March, 1931. Desiccated hog's stomach,v, 10 gm., q. d. for 17 days (Fig. 2-C).

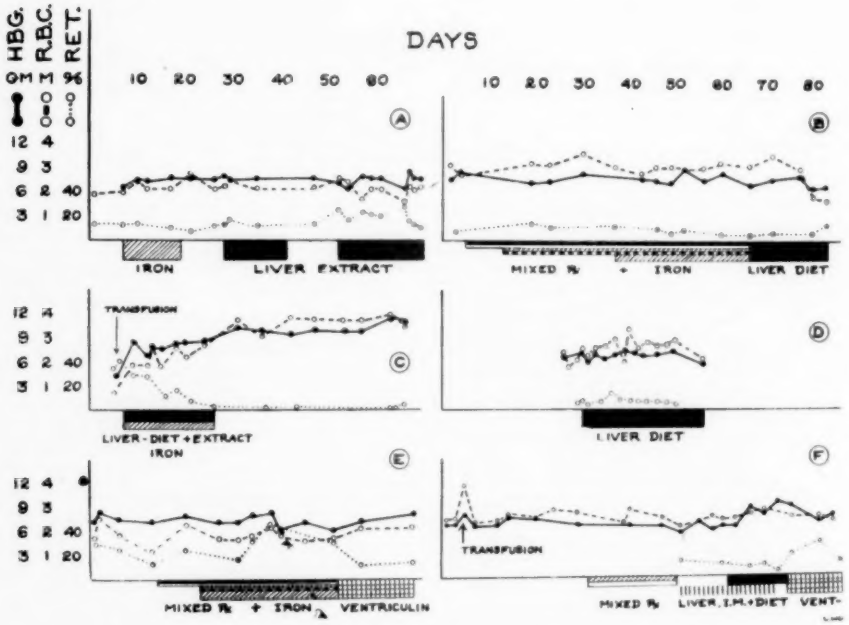


FIG. 3.—Chart showing the effect of various antianemic measures used in 6 cases of sickle-cell anemia.

August, 1931. Iron and ammonium citrate, 6 gm., q. d. for 12 days; 9 days later, liver extract,x, 60 cc., q. d. for 13 days; 11 days later, liver extract,x, 75 cc., q. d. for 18 days (Fig. 3-A). This was followed by a mixture of iron and copper,z, 45 cc., q. d. for 4 weeks (Fig. 2-F).

April, 1932. Pills of ferrous carbonate, 2 to 4 gm., q. d., for 12 days (Fig. 2-E).

May, 1932. Mixed treatment,j, 30 cc., q. d. for 13 days; 2 weeks later pills of ferrous carbonate, 4 gm., q. d. for 14 days (Fig. 2-D).

x Liver extract (Valentine) 30 cc. equivalent approximately to 227 grams (½ lb.) raw liver. It should be noted that the drugs given were not under the control of the author.

v Ventriculin (Parke-Davis).

z Iron and Copper (McKesson). Each fluidounce represents copper 0.057 gr. and iron 0.456 gr.

j "Jeculin" (Upjohn). Each fluidounce represents: fresh liver 2.66 ounces, orange juice concentrate 1.35 ounce, glycerinated extract of red bone marrow, 10 minims, iron and ammonium citrate 8 gr. and malt extract q. s.

Discussion. The response of the anemia to the various antianemic measures used (Figs. 1, 2 and 3-A), reveals no significant alteration. The minor fluctuations in values for erythrocytes, nucleated red blood cells, reticulocytes, hemoglobin and leukocytes during the treatment periods are of the same magnitude as those observed during the control periods. The number of sickled cells in the stained smears, and the capacity of the erythrocytes to sickle in moist preparations were not affected by the therapy used. Clinical phenomena, such as attacks of joint pain, abdominal crises, leg ulcers, and mild respiratory infections occurred during the treatment periods as well as during the non-treatment intervals. The blood picture was essentially the same at the age of 14 when the patient was first admitted to the hospital as it was for the next 4 years. The anemia was no more severe when the patient was sick in bed or during attacks of severe pain, than when she was symptom free and working. This case is representative of a type of sickle-cell anemia in which the symptoms are subject to marked remissions and exacerbations, but the anemia is chronic and fixed within rather narrow limits.

CASE 2.—R. C., male, aged 11, was admitted during an attack of acute arthritic pains. The red cell count was 3,110,000, the hemoglobin 7.9 gm. and the reticulocyte percentage 9. Mixed treatment,j, 12 cc., was started, and 8 days later increased to 30 cc., q. d. which was continued for 24 days. Pills of ferrous carbonate 2 gm., q. d. were then added and the combined medication given for 29 days, following which liver diet, 200 gm., q. d. was substituted, and continued for 17 days. There was no appreciable effect of these therapeutic measures on the anemia, in fact there was a tendency for the anemia to become worse (Fig. 3-B). The patient had a draining osteomyelitis sinus and also had swollen cervical lymph nodes, probably tuberculous, and these complications are to be given consideration in evaluating the lack of response.

CASE 3.—A. M., male, aged 24. Following the subsidence of an attack of severe lumbar pain with associated abdominal tenderness and rigidity, the patient was given, in addition to the usual hospital diet, 400 gm. of whole liver per day for 26 days with no alteration in hemoglobin, red blood cells or reticulocytes (Fig. 3-D).

CASE 4.—C. T., male, aged 8, gave a typical history of sickle-cell anemia. The red blood cell count was 1,790,000, hemoglobin 7 gm. and reticulocytes 32 per cent. Following a 10-day treatment with alkalies without effect on the anemia, mixed treatment,j, 12 cc., q. d. was given for 9 days, after which the dosage was doubled and pills of ferrous carbonate 2 gm., q. d. were added. After 1 month's trial on this combined therapy, desiccated hog's stomach,v, 30 gm., q. d. was substituted and continued for 18 days. There was no appreciable effect of any of these drugs on the level of the anemia (Fig. 3-E). The slight increase in reticulocytes is probably not significant.

CASE 5.—P. M., male, aged 12, was admitted during an attack of lobar pneumonia. Large ulcers of 2 years' duration were present on both legs. The red blood cell count was 2,420,000, hemoglobin 6.7 gm., leukocyte count 19,900. The anemia was of the normocytic, normochromic type. Free hydrochloric acid was present in the stomach contents. With the exception of a temporary improvement following a transfusion of 275 cc. of blood, there was no alteration in the degree of anemia under general

hospital care and supportive measures, although the clinical condition steadily improved. The use for 19 days of a mixture of cod-liver oil, iron and bone-marrow extract,m, 12 cc., q. d. was without effect. Subcutaneous liver extract,c, 1 ampule q. d. for 21 days, supplemented by a high caloric diet which included whole liver, 300 gm., q. d. for 13 days, and followed by desiccated hog's stomach,v, 10 gm., q. d. for 12 days produced no change in the blood picture (Fig. 3-F).

CASE 6.—W. T., male, aged 28, was admitted with severe abdominal symptoms which rapidly subsided. The red blood cell count was 3,100,000, hemoglobin 7.8 gm., reticulocyte percentage 8.2. Whole liver 450 gm., q. d. was given for 12 days with no significant alteration in the blood findings.

CASE 7.—B. L. H., female, aged 3, was admitted because of marked weakness and cachexia associated with bronchopneumonia. The past history was essentially negative. The red blood cell count was 700,000, hemoglobin 4.1 gm., reticulocyte percentage 29; leukocyte count 64,000, which when corrected for megaloblasts and nucleated red blood cells was 21,200. Typical sickled cells were not present in the stained smears, but moist preparations on standing revealed the sickle-cell phenomenon. The sickle-cell trait was also demonstrated in the father and in two siblings. Free hydrochloric acid was present in the stomach contents.

On account of the severity of the anemia and the apparent critical condition of the patient, transfusion of 230 cc. of whole blood was given on the second day, and daily medication consisting of whole liver, 200 gm., liver extract,x, 45 cc., and iron and ammonium citrate 1.5 gm. was started. The patient's clinical condition rapidly improved, the red blood cell count and hemoglobin values rose and the reticulocyte count precipitately dropped (Fig. 3-C). Coincidentally the primitive cells of the erythrocytic and granulocytic series disappeared from the circulating blood, and the leukocyte count returned to normal (Fig. 3-C). On the 19th day of treatment, severe diarrhea developed and medication was discontined. Improvement in the blood picture continued in absence of medication but soon reached a level of 3 to 4 million red blood cells and 9 to 11 gm. of hemoglobin, where it remained during the observation period. Further studies of the blood have not been possible.

Discussion. The favorable response following therapeutic measures in this case cannot be entirely attributed to the medications used, for there was no control period to indicate what would have happened had no medication been given, and the improvement in the respiratory infection rather than the antianemic measures used might have been the predominant factor in causing the return of the blood picture toward normal. This patient, whose anemia improved, differed from the 6 patients whose anemia remained stationary in that she was younger, the anemia was observed during its early stage, and typical sickled cells were absent in the stained smears. Cases of this type, which at one time give the characteristic picture of active sickle-cell anemia and then revert to a condition in which the sickle-cell trait is the only demonstrable abnormality are rare. The existence of such a type, and the possibility of spon-

m Myeladol (Upjohn). Each fluidounce contains: Cod liver oil 120 minims, glycerinated extract red bone marrow 10 minims, iron and ammonium citrate 4 gm., malt extract, q. s.

c Liver extract, subcutaneous (Chappel). Each ampule contains the active principle of 25 gm., of liver.

taneous remissions in any given case, should make one guarded in drawing conclusions as to the effectiveness of therapeutic measures.

Summary. Seven negro patients with sickle-cell anemia were treated with one or more of the following antianemic medications: whole liver, liver extract by mouth, liver extract subcutaneously, desiccated hog's stomach, bone-marrow extract, iron, and transfusion. In 6 cases the erythrocyte, hemoglobin and reticulocyte values, and the clinical condition following therapy did not significantly change. In 1 negro child with the sickle-cell trait, observed during an initial anemic crisis associated with bronchopneumonia, clinical improvement and improvement of the anemia followed transfusion and the administration of liver and iron.

There is a dearth of information concerning the natural course of sickle-cell anemia in all its varied manifestations, and the possibility of spontaneous remissions must be considered in the evaluation of favorable therapeutic responses. The effectiveness of any form of therapy in the treatment of sickle-cell anemia remains to be proved.

Appreciation is expressed to the clinical staff of the Memphis General Hospital for their coöperation, to Jaunita Bibb for technical assistance and to the manufacturers for furnishing without cost the drugs used in this investigation.

REFERENCES.

1. Sydenstricker, V. P.: Med. Clin. North America, 1929, **12**, 1451.
2. Yater, W. M., and Mollari, M.: J. Am. Med. Assn., 1931, **96**, 1671.
3. Leivy, F. E., and Schnabel, T. G.: Am. J. Med. Sci., 1932, **183**, 381.
4. Anderson, W. W., and Ware, R. L.: Am. J. Dis. Child., 1932, **44**, 1055.
5. Levy, J.: Ann. Int. Med., 1929, **3**, 47.
6. Brandau, G. M.: Arch. Int. Med., 1932, **50**, 635.
7. Torrance, E. G., and Schnabel, T. G.: Ann. Int. Med., 1932, **6**, 782.
8. Ching, R. E., and Diggs, L. W.: Arch. Int. Med., 1933, **51**, 100.

THE EFFECT OF LEUKOCYTIC CREAM INJECTIONS IN THE TREATMENT OF THE NEUTROPENIAS.

By Max M. Strumia, M.D., Sc.D.,

DIRECTOR CLINICAL LABORATORY, BRYN MAWR HOSPITAL; ASSOCIATE IN PATHOLOGY, SCHOOL OF MEDICINE AND GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

(From the Clinical Laboratory of the Bryn Mawr Hospital and the Department of Pathology of the University of Pennsylvania.)

The purpose of this paper is to present a preliminary report of the effect of intramuscular injections of leukocytic cream in cases of severe neutropenias and to describe a method for the separation of the leukocytic cream from the blood.

Nuclein therapy to increase the germicidal power of the blood in infections was advocated in 1893 by Vaughan, Novy and McClintock[1] and from time to time contributions on this subject have appeared in

the literature (Ames and Huntley,[2] De Paoli and Calisti,[3] and others). The therapy of neutropenia has been excellently reviewed recently by Doan[4] who has given extensive references to the subject, which will not be repeated here. Observations by Sabin,[5] Sabin, Doan, Cunningham and Kindwall[6] and Doan and Zerfas[7] brought out the fact that showers in the peripheral circulation of old non-motile polymorphonuclear leukocytes are soon followed by an increase of young neutrophils. These findings lend support to the theory that normally stimulation to new granulocytic cell formation is due to material liberated from the breaking down of old cells. Very likely the beneficial effect of transfusions in neutropenias is due to the introduction in circulation of such material. I personally feel that in view of the findings to be reported here it might be better to limit the conception of the effect of autolytic products of old cells to the maturation and release of new granulocytic cells rather than the multiplication of parent cells.

Recently the most successful attempt in the treatment of neutropenias has undoubtedly been the introduction of pentose nucleotides by Jackson, Parker, Rinehart and Taylor[8] in 1931. This substance, now available commercially, has been rather extensively used. In 69 cases of agranulocytic angina, malignant neutropenias and allied conditions Jackson, Parker and Taylor[9] report that 74 per cent of the cases treated with nucleotides recovered. They believe that the preparation was effective because of the favorable clinical and hematologic changes about the 5th day of treatment, and because the subsequent hematologic improvement in practically all cases followed the same pattern. The mortality in the cases treated with nucleotides is certainly lower than that of any other form of treatment yet devised. Doan[4] reports the following table of mortality in malignant neutropenia or agranulocytosis:

TABLE 1.—MORTALITY STATISTICS OF MALIGNANT NEUTROPENIA. (DOAN.)

Therapy.	Cases.	Deaths.	Mortality per cent.
Untreated	Many	...	90 or more
Miscellaneous therapeutic measures	178	133	74
Arsphenamin	33	24	72
Blood transfusion	53	34	64
Irradiation	64	34	53
Nucleotide	44	11	25

It would be entirely beyond the purpose of this paper to discuss the mechanism of action of all of these therapeutic measures. I wish, however, to point out the probability that Roentgen ray acts upon the bone marrow not by direct stimulation but through the intermediate destruction of a number of cells and liberation of disintegration products. This view is supported by the fact that, in the majority of cases treated by Roentgen ray, after the application

there is first a further lowering of the level of the granulocytes, to be followed in the favorable cases by an increase. There are, however, many cases of neutropenia, both of the agranulocytic type and in acute leukemias, that following even a single dose never recover from the further depression of the bone-marrow function.

It occurred to me from purely theoretical considerations that injection of leukocytes intramuscularly in cases of neutropenia might furnish such products of disintegration, containing large amount of nucleic acid salts in a form probably well tolerated and active. At first (1930 to the early part of 1932) the leukocytes were separated in very simple fashion. Citrated blood in large tubes was centrifuged for 15 to 20 minutes at high speed. The grayish layer thus formed between the supernatant plasma and the packed red cells was then skimmed off with a pipette, along with some of the plasma and some of the red cells, and injected intramuscularly. Because of the imperfect method of preparation the doses used in the first 3 cases (Cases 8, 9, 10 of this series) contained approximately ½ the number of leukocytes used in Cases 1 to 7, inclusive. As a matter of fact the first patient treated received first small doses of whole citrated blood, with little effect and much local discomfort.

Case 8.—G. V., a girl aged 13, had a chronic form of agranulocytosis with recurrent exacerbations. It is of interest to note that a lowering of the total leukocyte count occurred either during or a few days after the beginning of the menstrual flow. This phenomenon was also observed in Case 5 (Mrs. W. F. H.) by Dr. Klein and Dr. Neff and by Dr. Ellis in Case 6.

The relationship between menstrual period and acute attacks of agranulocytosis is of great interest, in view of the well known fact that the majority of cases of agranulocytosis occur in young and adult females. During one of these attacks, characterized by great prostration, ulcerations of the mouth, subfebrile temperature and bleeding from the nose, the patient received in 5 consecutive days intramuscular injections of leukocytic cream. Before treatment the leukocyte count was 1200 with 96 mature granulocyte per c.mm. After the 4th injection the total leukocyte count was 3350 with 435 mature granulocytes. Two days after the 5th injection the total leukocyte count was 4200 with 840 granulocytic cells and on the same day a new series of 5 daily injections was begun. After the 3d injection the total leukocyte count rose to 5700 with 3135 granulocytic cells. The ulcerations of the mouth at this point had healed and the temperature had returned to normal. Three days after the last injection, or 16 days after the first injection, the total leukocyte count was 6500 with 3315 granulocytes. Recovery or temporary improvement from previous acute attacks in this case, even less severe than the one here described, had always been much slower, the period being about 6 weeks or more for the improvement to manifest itself. The patient died recently of acute appendicitis.

Case 9.—A. M., the second patient treated, a white male, aged 51, was first seen by me 1 week after the onset of symptoms, when he had a septic temperature, with daily elevations to 102° to 103° F., a diffuse ulcerative stomatitis with considerable swelling of the cervical lymph nodes, profuse bloody diarrhea and great prostration. The total leukocyte count was 950 with no granulocytes. The count was repeated on the same day, the result being 870 total leukocyte count without any granulocytes being

seen in several slides. This patient received daily doses of leukocytic cream for 6 days. After the 4th dose the total leukocytic count was 2900 with 335 granulocytes. Next day the temperature returned to normal and the mouth ulcerations began to heal rapidly. Diarrhea with bloody stools however, continued and a second series of 5 daily injections was begun, 3 days after the last dose of the first series. After the 3d injection the diarrhea practically disappeared, the stools no longer contained blood and the total leukocyte count was 4700 with 1645 granulocytic cells. Two days after the last injection of the second series, or 14 days after the treatment was begun, the total leukocyte count was 6300 with 3786 granulocytes, and no clinical manifestations of the disease. This patient had no recurrence, and died recently of carcinoma of the colon.

CASE 10.—C. Q., a white woman aged 72, had suffered for years from hypertension and failing cardiac action. She complained of great weakness for about 15 days before the onset of the severe symptoms which included deep ulcerations of both tonsils, fetid breath, superficial ulcerations of the gums, with small hemorrhages and moderate swelling of the cervical lymph nodes. The temperature was septic with elevation up to 104° F. on the 2d day. That day the total leukocyte count was 1450 with 44 granulocytic cells per c.mm. On the 3d day from the onset of fever, the leukocytic cream injections were begun, the patient receiving daily injections for 7 days. After the 3d injection the total leukocyte count was 1680 with 201 granulocytic cells. Clinical improvement began the same day with progressive healing of throat ulcerations. Next day the temperature returned to normal. After the 5th dose the total leukocyte count was 2450 with 808 granulocytic cells, and 3 days after the last dose the leukocytic count was 5600 with 3416 granulocytic cells. A few days later, while convalescing, the patient developed signs of acute phlebitis of the right leg accompanied by a temperature elevation to 101.5° F. It is of great interest to note that the leukocytes at this point rose to 12,500 with 23 per cent young forms (rod-nuclears and metamyelocytes); that is, the patient had an adequate bone-marrow response to infection. A blood culture taken at this time yielded no growth and patient slowly made complete recovery. The patient has had no new attacks and is at present living and well.

In the early part of 1932 in connection with work on phagocytosis at the University of Pennsylvania, I devised a method of separation of leukocytic cream from the blood as follows:

Method. Withdraw the blood from the vein of the donor into citrate solution not less than 150 cc. Divide the blood in large tubes and centrifuge at high speed for 30 minutes. Carefully withdraw the clear supernatant plasma, part of which is kept for the preparation of leukocytic emulsion later. With a large mouth pipette and a rubber bulb remove carefully the buffy layer of leukocytes which has formed on the surface of the packed red cells. Do that for each tube and transfer the material to a Babcock cream tube. Add to this enough of the packed red cells to bring up well in the neck the surface of the fluid. Centrifuge again for 20 minutes at high speed. The leukocytes will now rise to the top. There are usually three well defined layers: (1) clear plasma; (2) suspension of leukocytes and platelets; (3) leukocytes mixed with some red cells. This last layer has been found to be richer in polys, while the topmost layer contains more lymphocytes. Draw off with a large-mouth capillary pipette this material, removing also the top layer of the packed erythrocytes. Suspend this material with plasma so as to make for each 100 cc. of blood used 5 to 10 cc. of suspension. The material is used intramuscularly. As a rule, with high speed of the centrifuge the volume of the packed leukocytes is 1.6 per cent of the amount of blood used.

and the suspension contains about $\frac{2}{3}$ of the leukocytes present in the blood used. In smears of the suspension, the leukocytes appear very well preserved. It is desirable to check with a smear, or better, a cell count, that the suspension prepared is adequately rich in leukocytes. It is essential to separate the leukocytes from the blood as early as possible after the withdrawal of the blood from the donor. If for some reason the blood must be kept overnight, twice the amount of citrate should be used. The leukocytes thus prepared remain well preserved for a period of 7 days at least, although I have never used them after 5. Of course strict aseptic technique

FIG. 1.—A Babcock cream bottle, showing from top to bottom small layer of plasma (dark), leukocytic cream (light) and packed erythrocytes.

must be employed. Another important point is to remove as much of the plasma as possible after the first centrifugation and to have the topmost layer of the material transferred in the Babcock cream bottle as high as possible in the neck. If for some reason (deficiency of red cells) this is not possible, the surface of the fluid may be brought to the proper point by introducing in the Babcock cream bottle sterile glass beads. If the material necessary is ready at hand the whole procedure for 500 cc. of blood can easily be accomplished in 2 hours or a little less.

The citrate solution, as anticoagulant, is prepared by dissolving 20 gm. of sodium citrate in enough sodium chlorid solution to make 100 cc. The

sodium chlorid solution percentage is 0.85. This solution contains for each cc. 200 mg. of sodium citrate, which is sufficient to prevent coagulation of 50 cc. of blood.

For all of the cases from 1 to 7 inclusive, each dose of leukocytic cream was prepared from 100 to 150 cc. of blood, unless otherwise stated. The intramuscular injection of this preparation has never given rise to reaction, neither local nor general, save slight local pain, even when repeated for a long period of time.

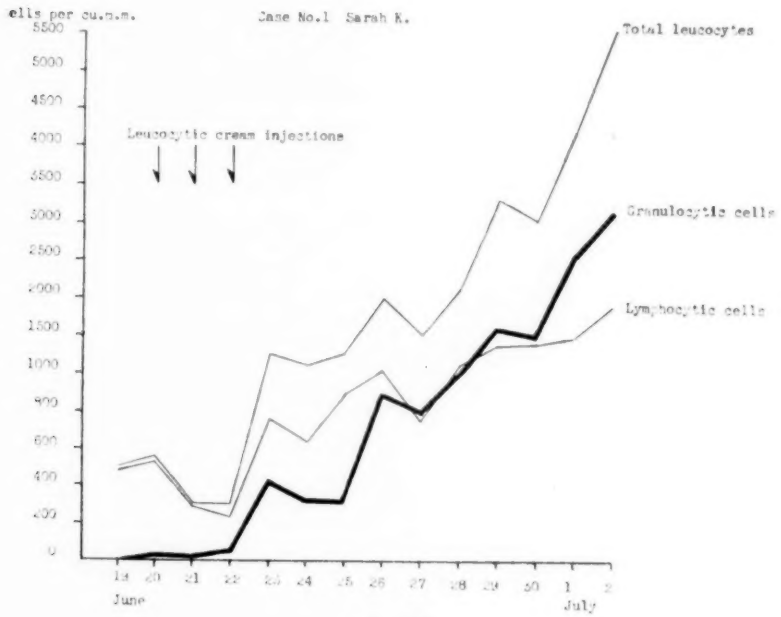


CHART I.

CASE 1.—S. K., a white, married woman aged 52, was admitted to the Bryn Mawr Hospital on June 18, 1932, on the service of Dr. H. W. Taylor with complaint of sore throat and weakness. The patient, 2 weeks prior to admission, had generalized body aching, followed by sore throat and subfebrile elevation of temperature. The patient did not recall any previous attacks of similar nature. On admission she appeared acutely and severely ill with profound prostration, stomatitis and pharyngitis, and temperature of 103° F. The blood examination on admission gave the following results: Hemoglobin, 11.84 gm.; erythrocytes, 3,040,000; leukocytes, 550; platelets, 354,000. The differential count showed: metamyelocytes, 1 per cent; rod-nuclears, 2 per cent; lymphoblasts, 2 per cent; prolymphocytes, 10 per cent; lymphocytes, 83 per cent; monocytes, 1 per cent; Tuerck cells, 1 per cent. The total content of granulocytic cells per c.mm. of blood (young cells only were seen) was therefore 15. Successive blood examinations and the dates of leukocytic cream injections are given on Chart I. A few purpuric spots appeared on her extremities shortly after admission, and on June 21 a pustular eruption developed around the anus.

For several days she was profoundly drowsy. Definite clinical improvement began about June 28, when the temperature returned to normal and remained so except for a slight subfebrile elevation later, during the course of a small abscess of the right foot accompanied by mild cellulitis of the leg. The patient was discharged in good condition on July 23 with a leukocyte count of 7400 and the following differential: rod-nuclears, 3 per cent; neutrophilic polys, 73 per cent; lymphocytes, 20 per cent; monocytes, 4 per cent. On August 19, 1932, there was a new mild attack of neutropenia with a leukocyte count of 3200 and 1236 granulocytic cells per c.mm. This attack was not accompanied by clinical symptoms and the patient quickly recovered without treatment. The patient is at present (June, 1933) living and well.

In addition to 3 injections of leukocytic cream the patient received 3 blood transfusions on June 21, 23 and 25, citrated blood being used in the following doses: 450 cc., 300 cc. and 550 cc. Pentose nucleotides injections were also used intramuscularly in daily doses from June 24 to June 30. It is seen, however, from Chart I that a sharp increase of the granulocytic cells of the blood occurred within 48 hours of the first injection of leukocytic cream, and that fully 24 hours before the first dose of pentose nucleotides was given the granulocytic cells had increased to 415 per c.mm. and the total leukocytes to 1250. If, in addition, one considers the fact that with pentose nucleotides a rise in the leukocyte count usually appears in the 5th day after the first dose, we may safely say that pentose nucleotides did not have anything to do with the sharp and early rise of the granulocytes which occurred after the injection of leukocytic cream and transfusions. It is possible that the later increase in leukocytes which occurred on the 28th and following days might have been at least partly due to the pentose nucleotides therapy.

Case 2.—A. McC., a white, single woman, aged 36, was admitted to the Bryn Mawr Hospital on October 14, 1932; under the care of Dr. J. J. Sweeney and myself with complaint of sore throat, swelling of the face and neck, fever and severe general malaise. Two weeks prior to admission patient had suddenly developed swelling of the face and neck accompanied by sore throat with great prostration and febrile rise in temperature. The patient did not recall any similar attack. On admission the patient was gravely and acutely ill with intense drowsiness, swelling of the face and neck, severe diffuse stomatitis and pharyngitis with superficial ulcerations, covered with fibrinous exudate. The temperature was 102. The blood count gave the following results: hemoglobin, 14.55 gm.; erythrocytes, 3,900,000; leukocytes, 1100; platelets, 437,000, and the differential showed metamyelocytes, 0.5 per cent; rod-nuclears, 10 per cent; polys, 31.5 per cent; lymphocytes, 33.5 per cent; monocytes, 16 per cent; eosinophils, 0.5 per cent; basophils, 1.5 per cent; hemohistioblasts, 0.5 per cent; prolymphocytes, 5.5 per cent; monoblasts, 0.5 per cent. The granulocytic cells, 462 per c.mm., represented approximately $\frac{1}{10}$ of the normal content. On October 15, 50 cc. of whole blood were given intramuscularly. On the 17th the first dose of leukocytic cream was given. This was followed next day by a return of the temperature to normal, a distinct clinical improvement and a sharp increase of the granulocytes in the blood. The clinical improvement with rapid healing of the mouth and throat continued uninterruptedly, the patient being discharged on October 26 in good condition and with the following blood picture: leukocytes, 3900; myelocytes, 1 per cent; metamyelocytes, 2 per cent; rod-nuclears, 15 per cent; polys, 54 per cent; prolymphocytes, 3 per cent; lymphocytes, 11 per cent; monocytes, 12 per cent; eosinophils, 1 per cent; Rieder cells, 1 per cent; the total number of granulocytic cells per c.mm. being therefore 2847.

Following the patient's discharge from the hospital, the blood picture

improved steadily until on December 29 it had returned to within normal limits. In this case no other therapeutic measure was employed except the 1 injection of whole blood and the 6 successive injections of leukocytic cream. The patient was followed with weekly and later fortnightly blood examinations. For 6 months the blood count remained practically normal except for a slight increase of the young granulocytes (rod-nuclears 7 to 8 per cent). On May 5, 1933, the total leukocyte count dropped to 4400 with 3212 granulocytic cells per c.mm. of blood. On May 20 the total leukocyte count was 3700 with 2775 granulocytic cells. The patient at this time complained of increasing although not severe weakness. On the 24th of the same month leukocytic cream injections were given for 5 consecutive days. Two days after the 1st injection the total leukocyte count had risen to 5300 and the total number of granulocytic cells to 3710, the patient feeling distinctly stronger. On May 29, the day after the last injection, the total leukocyte count was 5250 with 3517 granulocytic cells per c.mm. of blood. This case is still under observation.

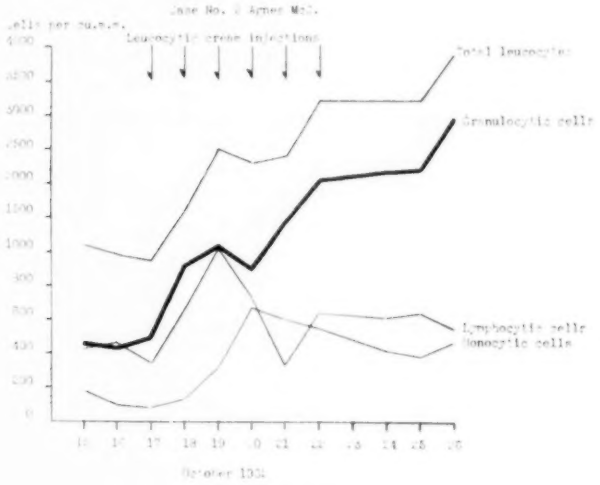


CHART II.

CASE 3.—G. B., a white male, aged 41, was admitted to the Bryn Mawr Hospital on February 13, 1933, under the care of Dr. Klein and Dr. Taylor, with complaint of fever, weakness, and soreness of the mouth. On January 15, 1933, the patient had complained of moderate sore throat with severe joint pains and backache with a temperature elevation to 103° F. Sore throat and pains improved after 3 days of illness but for several more days the patient had an afternoon temperature rise to 100° to 102° with occasional night sweats. About January 8 a blood examination was done with the following result: hemoglobin, 14.5 gm.; erythrocytes, 4,340,000; leukocytes, 8800; neutrophilic polys, 34 per cent; lymphocytes, 61 per cent; monocytes, 3 per cent; eosinophils, 1 per cent; Tuerck cells, 1 per cent. Of the polymorphonuclear leukocytes 24 per cent were young forms. He returned to his business on January 24 feeling much better but still having a daily temperature elevation to 99° to 99.3°, in the afternoon. On February 11 he noticed soreness of the gums, and on February 12, had a temperature elevation to 103° with generalized pains and weakness. The leukocyte count at this time was 4500. On admission the temperature was normal

and there was a diffuse acute stomatitis with considerable redness and swelling of the gums. The blood count on admission showed leukocytes, 3900; metamyelocytes, 0.5 per cent; rod-nuclears, 1.8 per cent; polys, 0.5 per cent; prolymphocytes, 4 per cent; lymphocytes, 85.4 per cent; monocytes, 6 per cent; eosinophils, 1.3 per cent; Rieder cells, 0.5 per cent. There were numerous shadow cells and the total content of granulocytic cells was 160 per c.mm. The successive blood examinations and the dates of injections of leukocytic cream are summarized on Chart III.

Following the first injection of leukocytic cream the lesion of the mouth very rapidly improved along with the increase of the granulocytic cells in the blood. At the time of discharge on February 22 the mouth had entirely healed and blood count showed leukocytes, 6200; rod-nuclears, 10 per cent; polys, 60 per cent; prolymphocytes, 3 per cent; lymphocytes, 18 per cent; monocytes, 6 per cent; eosinophils, 3 per cent. The total granulocytic cell content per c.mm. was 4526.

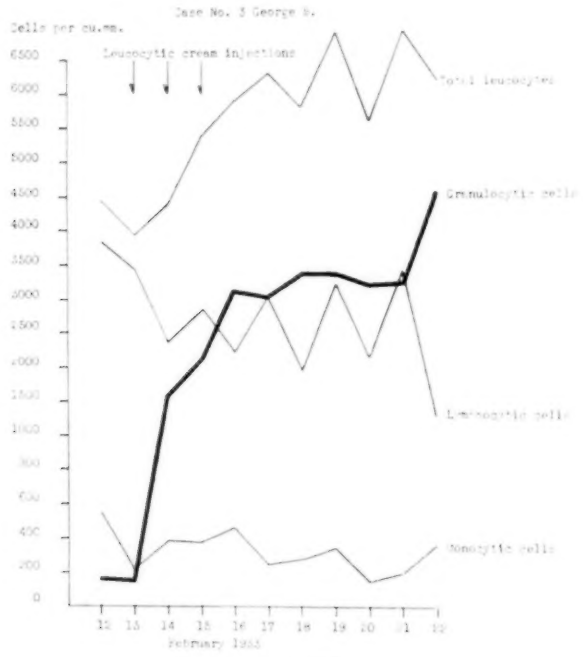


CHART III.

The patient has been under constant observation since discharge from the hospital and his health has remained good until present time and his blood picture normal except for a very slight lymphocytosis.

CASE 4.—Mrs. P. R., a white, married female, aged 34, was admitted to the Bryn Mawr Hospital April 11, under the care of Dr. H. C. Earnshaw, with complaint of severe sore throat, high fever and general malaise. On April 5 she had chill followed by very severe general prostration and headache. This continued next day but on the 7th she felt better. On April 9

she had a severe chill early in the morning followed by general malaise and severe sore throat. The temperature was then 104° F. and remained high with a septic curve up to the time of admission to the hospital. On April 10 the leukocytes were 3400 and the differential showed hemohistioblasts, 1 per cent; prolymphocytes, 7 per cent; lymphocytes, 59 per cent; monoblasts, 1 per cent; monocytes, 31 per cent; basophils, 1 per cent. No neutrophilic cells were seen on several smears.

On admission to the hospital at 10 A.M. the patient appeared acutely ill, with a temperature of 101°, a diffuse swelling of the neck, especially on the left side, due to enlarged lymph nodes and severe prostration. There were two grayish deep-seated ulcerations involving both tonsillar regions, covered by necrotic sloughs. Small ulcerations were scattered over the gums. The leukocytes were then 1400 per c.mm. and only 1 promyelocyte was

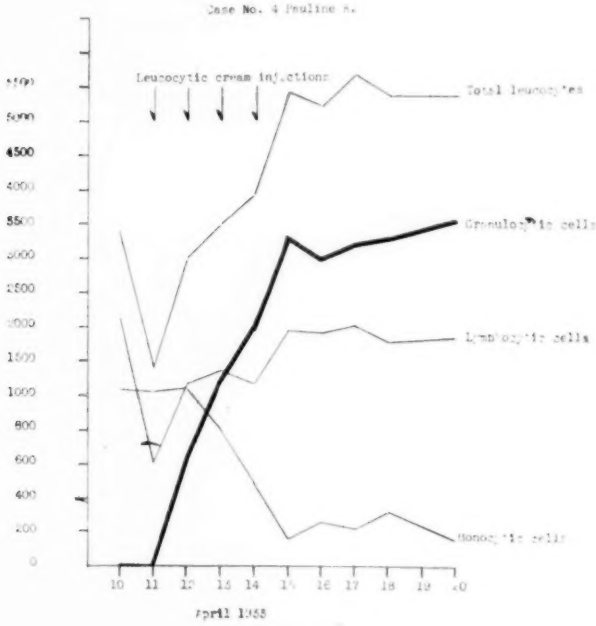


CHART IV.

seen in several smears. The first dose of leukocytic cream was given the same day at 5 P.M. and shortly after, a transfusion of 250 cc. of citrated blood was given, after which the patient had severe reaction with sharp rise in temperature. The next morning the patient felt much better and the temperature had returned to normal. The leukocyte count sharply increased to 3000 per c.mm. with a considerable shower of mature and young granulocytic cells. The throat lesion appeared in form of a white adherent membrane covering the whole uvula and both tonsillar regions. Although the mouth was still sore the patient felt much more comfortable. A second leukocytic cream injection was given to the patient April 12 at 10.30 A.M. and the clinical condition continued rapidly to improve along with the blood picture, the temperature remaining normal from April 12 on. Healing of the mouth lesion went on very rapidly. The blood picture and the date of leukocytic cream injections are summarized in Chart IV.

The patient was discharged from the hospital on April 24 in excellent general condition, the mouth lesions entirely healed, and with the following blood picture: Hemoglobin, 14.9 gm.; erythrocytes, 4,220,000; leukocytes, 5300; rod-nuclears, 3 per cent; neutrophilic polys, 56 per cent; prolymphocytes, 4 per cent; lymphocytes, 31 per cent; monocytes, 2 per cent; eosinophils, 1 per cent; basophils, 3 per cent; or 3339 granulocytic cells per c.mm. of blood.

CASE 5.—Mrs. W. F. H., aged 47, was admitted to the Presbyterian Hospital on April 15, 1933, on the service of Dr. Thomas Klein, with chief complaint of soreness of gums with ulcerations, soreness of the tongue, pharyngitis with ulcerations, fever, weakness, and nervousness. Three weeks prior to this attack the leukocyte count was normal, although 3 or 4 days prior to this count the symptoms stated above had begun. The day before admission the leukocyte count was 1250 with 4 young polys and 96 lympho-

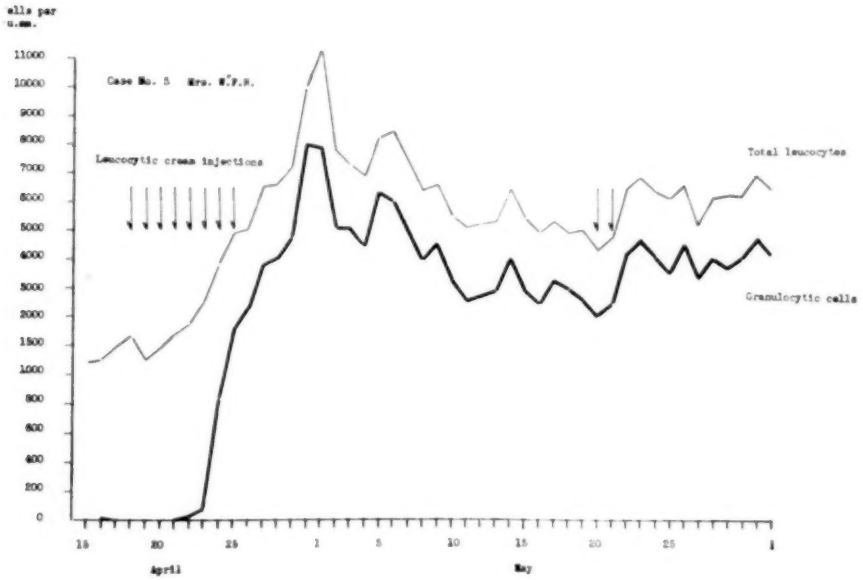


CHART V.

cytes. The history reveals that the patient had a similar attack 2 years before. She recovered from the first attack which was milder than the present, the therapy employed being sodium cacodylate hypodermically, and rest. After this illness the white cell count dropped at each menstruation to about 3000 with a percentage of polys of about 17. She recovered spontaneously from these attacks. For the past 6 months the count has been approximately normal.

This patient was operated upon in 1908 for hyperthyroidism and in 1930 had symptoms again, when she received light Roentgen ray therapy. This made conditions worse and she was operated upon again. In 1930 to help menopausal symptoms a light Roentgen ray dose was given. Shortly after this she had her first attack of neutropenia. It would appear that she is highly sensitive to Roentgen ray.

On admission on April 15, the temperature was 100° F., pulse 116, respira-

tion 24. The leukocyte count was 1200, no granulocytes being present (100 per cent lymphocytes). Leukocytic cream from 100 cc. of blood was prepared. This was divided in 8 doses of 10 cc. each and an initial dose of 5 cc. was used on the 15th. This dose was obviously much too small. Sodium cacodylate in the dosage of 2 grains hypodermically was given once a day for 15 days, starting with the 15th. On the 17th, 18th, 19th and 20th she had severe daily chills with rise of temperature up to 103.2°. On the 18th of April the first regular dose of leukocytic cream was given. Daily doses of leukocytic cream were continued for 8 days. Granulocytes reappeared in the blood 3 days after the first injection, and thereafter very rapidly increased and 7 days after the first dose, that is, on April 25, the total leukocyte count was 4900 and the granulocytic cells 1764. Chart V summarizes the hematologic picture of this patient for the period of her stay in the hospital.*

From Chart V it will be noted that the total leukocyte count after reaching a peak of 11,250 on May 1, with a total neutrophilic cell count of 7875 per c.mm., slowly dropped until on May 20 the total leukocyte count was 4300 with 2021 neutrophilic cells. The patient received 1 dose of leukocytic cream on May 20 and 1 on May 21. On May 22, that is, 2 days after the first dose, the total leukocytic count had risen to 6450 and the total number of neutrophilic cells to 4128, per c.mm. The patient's temperature had dropped to normal and remained normal thereafter, on the 24th of April, that is, 6 days after the first large dose of leukocytic cream was given. On April 28 she was out of bed and able to walk, the mouth had healed entirely and the patient felt altogether well. On May 8 the patient had returned to practically all normal activities of life and was discharged in good condition from the hospital on June 2. The point of great interest in this case as already noted is the coincidence of neutropenia with menstrual flow after the first severe attack.

Case 6.—Mrs. E. P. B., aged 30, was a robust white woman, who had had no febrile attacks within the past 3 years. During the past winter there had been repeated attacks of sinus pains out of proportion to the physical signs. The present illness had a sudden onset on the evening of March 25, with pains in the throat, ears and a temperature elevation to 103° F. There were mild ulcerations of the mouth, mostly peridental. The temperature subsided gradually until on March 28 it was 100° F., at which time a morphologic blood examination gave the following result (average of 2 determinations): total leukocytes, 2175; myelocytes, 0.5 per cent; young neutrophils (rod-nuclears and metamyelocytes), 14 per cent; mature neutrophilic polys, 6 per cent; eosinophils, 2 per cent; basophils, 1 per cent; monocytes, 11.5 per cent; lymphocytes, 65 per cent (511 total granulocytic cells per c.mm.). The diagnosis of agranulocytic angina was made, and blood transfusions were given on March 28, 29, and 30, totaling 1250 cc. A dose of pentose nucleotide was also given on March 30, but the reaction was so severe that it was not repeated. The behavior of the hematologic picture is summarized in Chart VI. The small peridental ulcerations healed and the patient seemed to be making a slow recovery, when a relapse occurred about April 25, 6 days after the menstrual flow. The previous attack had also been shortly preceded by the menstrual period. The second attack was much more severe with extensive necrotic mouth ulcerations, bleeding from the gums, vomitus of blood with large pieces of gangrenous tissue, temperature elevation to 105.3° F. On April 27 the blood picture was total leukocytic count 2250, no granulocytic cells, lymphocytes 83 per cent, monocytes, 17 per cent. Blood transfusions totaling 2020 cc. were given each day from April 25 to April 30; the leukocytic cream injec-

* I am much indebted to Dr. Klein, Dr. Neff and Dr. Fowler for their kindness in furnishing me the material concerning this case.

tions were begun also on April 26, and continued as illustrated in Chart VI, each dose of leukocytic cream corresponding to 150 cc. of blood. The rise of granulocytic cells began on the 28th, 2 days after the first dose of leukocytic cream and the first transfusion, when the total leukocytic count was 4000 with 120 granulocytic cells and continued rapidly until 5 days after beginning of treatment (April 30) the total leukocytes count was 5550, with 1276 granulocytic cells. The temperature steadily declined returning to normal shortly after, and massive sloughing of the mucosa of the mouth and upper digestive tract occurred.

On May 6 patient had another relapse but much milder, with no temperature elevation, and very superficial mouth ulcerations. It is important to note that this relapse was immediately preceded by a 2-day discontinuation of the leukocytic cream injections. Leukocytic cream injections were resumed, patient rapidly recovering from the second attack. The leukocytic cream injections were discontinued on May 24 for 4 consecutive days, this being immediately followed by another relapse with recurrence of

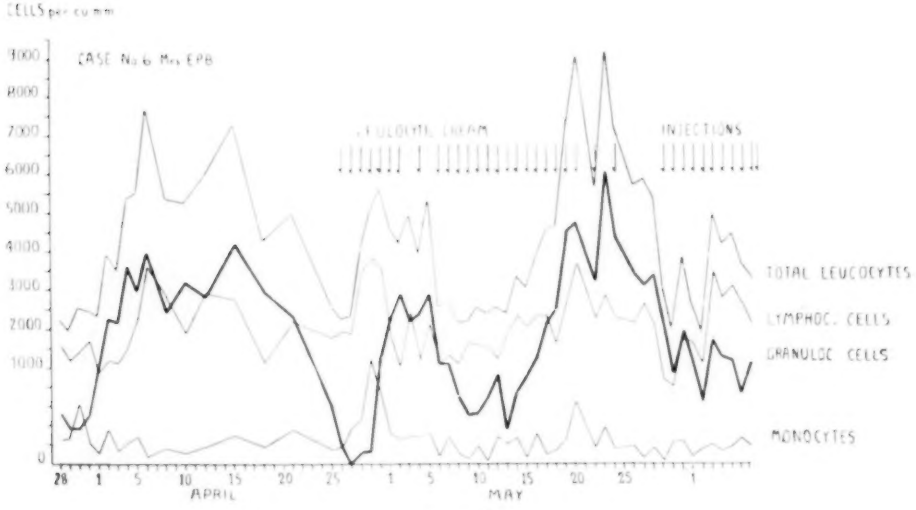


CHART VI.

infiltration and congestion of the gums far less severe than on previous occasions, and the elimination of a bone sequestrum left by the second severe attack. On June 3 the patient vomited a fairly good amount of fresh blood and on June 4, 5 and 6 there was vomitus with a small amount of chocolate blood. The leukocytic cream injections were resumed on May 29, and although the hematologic response was not as prompt as in previous occasions, the general condition as well as the mouth lesion improved greatly from June 3 on, she being generally much better than during any of the previous attacks. It is to be noted also that in the two relapses after the leukocytic cream was used, the total granulocytes did not go under 600 per c.mm. and that fever did not return. This third attack coincided with the menstrual flow, which began on May 24 and lasted for 5 days.*

* I am indebted for the notes on this case to Dr. Ellis, under whose care the patient has been, and to Dr. Belk, who furnished the laboratory data. She is still under treatment.

NOTE.—The count on June 12 on this patient after resumption of leukocytic cream injection gave the following results: Total leukocytic count, 5700; granulocytic cells per c.mm., 2451; lymphocytic cells per c.mm., 3192; monocytes per c.mm., 57.

CASE 7.—H. R., a man, aged 37, was admitted to the Jefferson Hospital on March 10, 1933, on the service of Dr. Harold Jones. At this time the patient complained of fatigue, pain over frontal sinuses, pallor and slight cardiac palpitation. His physical examination also showed severe visible pulsation in right side of neck and some enlargement of the submaxillary lymph glands. December 22, 1932, he had an attack of "grippe." He was forced to get out of bed because of illness of his wife but felt extremely weak. He returned to bed on the same day and remained there for 1 week. After this he felt better for awhile. On January 25, 1933, he consulted a physician, who remarked the pallor. Blood count showed red blood cells, 2,000,000. He was given liver and fresh vegetable diet, iron and arsenic, which treatment was continued until February 22, 1933, when a blood count showed no improvement. He was then referred to Dr. Jones and sent to the hospital. The patient had noticed slight shortness of breath on exertion and some cardiac palpitation for 2 months before admission. On admission to the hospital the temperature was 99° F. On March 19 and following days there were daily elevations up to 103.2° F. The temperature steadily but slowly decreased after March 25, returning to normal on April 8 and remaining so thereafter. Ulcerative lesions of the lips appeared on March 30, and a hard painful swelling of the rectum started on March 25, which on incision yielded small amount of bloody serum. This patient received 9 doses of pentose nucelotides from March 25 to March 30, 7 leukocytic cream injections were given from March 31 to April 7, and whole blood transfusions from 160 to 220 cc. on March 24, April 5, 10, 13, 17, 22, 26 and May 1, 3, 8, 12, 16, 20, 23 and 26. A sharp increase of the total leukocyte count occurred as follows: March 30, 1250; 31st, 2250; April 1, 5200; 3rd, 3100; 4th, 5200; 5th, 5900; 6th, 7600; 7th, 10,900. The differential count on April 1 showed a considerable increase of immature and mature granulocytic cells, but this did not continue, the bulk of the cells counted in successive days being erythroblasts, basophilic and eosinophilic. The clinical condition, however, greatly improved, and the rectal lesion spontaneously resolved and ruptured, healing completely. The patient is at present out of the hospital, still showing a severe neutropenia. The complexity of the case and the multiplicity of therapeutic measures employed do not allow any conclusion as to the effect that the injections of leukocytic cream may have had on the course.

Summarizing the effect of the leukocytic cream injections in 10 cases of agranulocytosis, I may state that in Case 1 an acute case, severe both clinically and hematologically, a sharp increase of granulocytes occurred within 48 hours of the first injection of leukocytic cream and continued thereafter, although only 3 injections were given. In Case 2, an acute case clinically severe but hematologically showing less severe neutropenia, the increase of the granulocytes occurred 24 hours after the first injection of leukocytic cream, and the hematologic and clinical improvement proceeded rapidly and uninterruptedly thereafter. This patient, 6 months after the first attack, had a mild hematologic relapse which again responded within 48 hours to the leukocytic cream injection. In Case 3, acute, clinically of moderate severity but with severe neutropenia, the increase in the granulocytic cells occurred within 36 hours, with a rapid and continuous improvement thereafter. In Case 4, acute, very severe both clinically and hematologically, the increase in the number of granulocytes in the circulating blood occurred within 24 hours of the first injection of leukocytic cream along with clinical improvement,

the patient's condition as well as the hematologic picture improving continuously and rapidly thereafter until complete recovery. In Case 5, in a second attack of great severity both clinically and hematologically, the hematologic and clinical response to the leukocytic cream injections occurred 3 to 4 days after the first injection and continued thereafter rapidly and continuously along with the clinical improvement. A mild hematologic relapse during the convalescence, without clinical symptoms, responded within 48 hours from the first of two leukocytic cream injections. In Case 6, an extremely severe case both hematologically and clinically, of the acute recurrent type, as long as leukocytic cream injections were kept up the hematologic picture remained fair and the patient free from symptoms, but discontinuance of the leukocytic cream injections was followed by relapse, far less severe however than those previous to the leukocytic cream injections. This patient is as yet under treatment and will be fully reported by Dr. Ellis. In Case 7, one of great severity both clinically and hematologically, the effect of leukocytic cream injections was doubtful. Case 8, one of chronic type with recurrent exacerbations, was treated with somewhat smaller doses of leukocytic cream but responded nevertheless within 3 days with a sharp increase of the granulocytic cells, the hematologic and clinical improvement continuing thereafter without interruption. In Case 9, a case of acute primary attack, severe both clinically and hematologically, hematologic and clinical improvement occurred within 3 days of the first dose of leukocytic cream and continued thereafter until complete recovery. Case 10, an acute primary attack, clinically and hematologically fairly severe, responded clinically and hematologically to the injections of leukocytic cream within 48 hours of the first dose with improvement progressing steadily thereafter to recovery.

In Case 1 pentose nucleotide injections were given when response to the leukocytic cream injection was already fully established. Case 2 received no other treatment except the leukocytic cream injections. Cases 3, 8, 9 and 10 likewise received nothing but leukocytic cream injections. Case 4 received leukocytic cream injection with a single small transfusion. Case 5 received leukocytic cream injections and hypodermic injections of sodium cacodylate. Case 6 received transfusions at the beginning of the treatment along with leukocytic cream, thereafter leukocytic cream only. Case 7, as stated in the history of the case, received leukocytic cream, transfusions and pentose nucleotides. It appears, therefore, that in agranulocytosis, both in single acute attacks or in recurrence, the leukocytic cream injections were followed by an increase of circulating granulocytic cells along with marked clinical improvement, in 9 out of 10 cases in which it was used. The clinical response and the hematologic improvement have been on the whole strikingly parallel and have progressed continuously after they have begun. The response occurred as a rule from 1 to 3 days after the first dose.

In all of the cases thus treated the hematologic response was characterized by an early shower of young granulocytes and later progressive increase of the mature polymorphonuclears.

In any work claiming results for new therapeutic measures it is of course of prime importance to furnish adequate controls. This is in all cases very difficult and particularly difficult with a relatively uncommon disease, such as agranulocytosis. Naturally all the cases that have recently come to my observation have been treated with leukocytic cream injections. In view of the known high mortality in this disease one is not justified in withholding any treatment that offers promise of being beneficial. In the records of the Bryn Mawr Hospital from 1928 up to the present, in addition to the cases already reported, there is only one ascertained case of agranulocytosis. This was a woman, Mrs. M. B., aged 27, who on January 1, 1929, had an attack of grippe. About a month later the patient had an attack of sore throat with fever and malaise. On February 8 she was admitted under the care of Dr. Councill and Dr. Ellis. This time she had severe ulcerations of the throat, febrile irregular temperature and a severe neutropenia with granulocytic cells as low as 100 per c.mm. of blood and the total leukocytic count considerably below 1000. During this first attack the patient received 12 blood transfusions, totaling 2160 cc., 7 Roentgen ray treatments and liver extract. Patient was readmitted to the hospital on June 25, 1929, with a severe relapse. During this relapse the temperature was constantly above 103°, reaching 106° on one occasion, the total leukocyte count was always below 900, being as low as 200, and no polymorphonuclears were seen in any of the numerous smears examined. The patient had severe peridental necrosis, developed signs of pneumonia, and died July 3. During the second attack she had received 5 doses of Roentgen ray and 11 blood transfusions, totaling 2700 cc. (This case also will be reported in detail by Dr. Ellis.)

Other cases that I have had occasion to see have been variously reported. In addition to the statistical data of Doan, previously referred to, Fitz-Hugh and Comroe[11] have reported 18 well studied cases, 15 of which died. Dameshek and Ingall[10] reported 9 cases of agranulocytosis of which 7 died. Considering the fact that agranulocytosis is not a disease entity and that practically no 2 cases run exactly alike, it becomes absolutely impossible to control properly the therapeutic effect of any material. Inasmuch as the purpose of this paper is merely to present facts concerning the action of leukocytic cream injections, and the method for the preparation of this leukocytic cream rather than claim specific or non-specific virtues for it in the treatment of agranulocytosis, the lack of an adequate control series is of less moment. What these patients would have done without the injections of leukocytic cream is purely a matter of speculation. Unquestionably some of the milder cases would have recovered spontaneously; the spontaneous

recoveries are as a rule, however, slower than those described here. On the other hand, extremely acute fulminating cases are probably not helped by any therapeutic measure.

In addition to the cases of agranulocytosis, leukocytic cream injections have been used in a small number of other forms of neutropenia. Three of these miscellaneous cases are presented here.

Miscellaneous Cases Treated with Leukocytic Cream. CASE A.—Miss M. B., aged 14, a case of acute lymphoblastic leukemia, admitted to the Bryn Mawr Hospital on May 2, 1933, on the service of Dr. Harvey, showed a constant neutropenia and was treated with 4 separate series of leukocytic cream injections. Accompanying table shows that each one of these series of injections was followed by a sharp increase in the number of circulating granulocytes. The number of these cells also very sharply dropped, usually within 48 hours of the last injection. This case will be

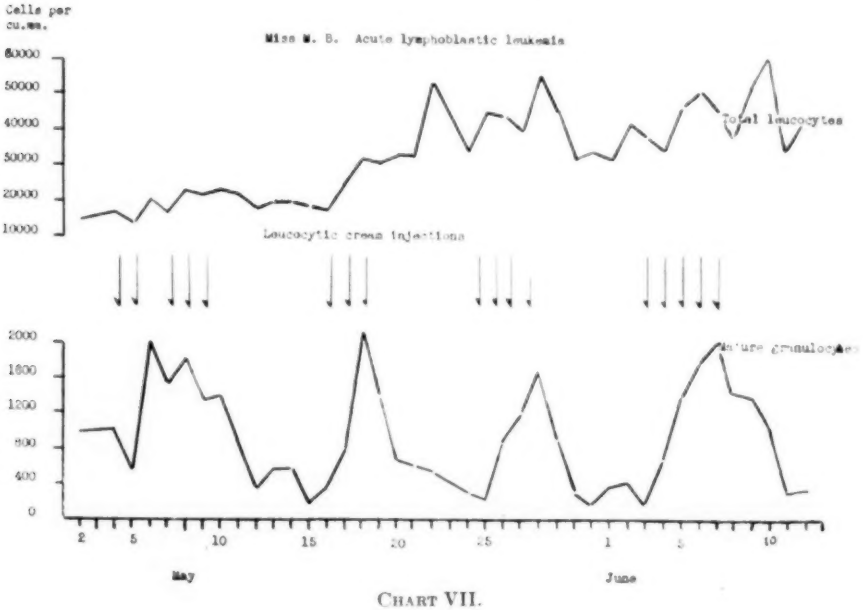


CHART VII.

reported in detail later, but it is interesting to notice that the patient has been free so far from the mouth infection so common in this disease, and that superficial ulcerations of the mouth and slight oozing of blood which occurred on June 1 rapidly disappeared when following leukocytic cream injections the granulocytic cells in the circulating blood increased from less than 200 to over 2000 per c.mm. in a few days.

CASE B.—Mrs. M. H., was admitted to the Bryn Mawr Hospital May 8, 1933, under the service of Dr. Harvey and later transferred to the service of Dr. Billings, with a diagnosis of bleeding carcinoma of the transverse colon, which was later confirmed by operation and tissue examination. The blood picture of this patient was carefully followed for 4 days prior to the leukocytic cream injections. For the 4 days preceding the first inoculation of leukocytic cream the average of the total leukocyte count was 3562 and the total granulocytic count 2365 per c.mm. with small daily variations.

Two doses of leukocytic cream were given on May 12 and 13. On May 13, within 24 hours of the first injections, the total leukocyte count was 4800 and the number of granulocytic cells 3792. This improvement continued for 3 days, thereafter slightly and slowly decreasing.

CASE C.—Baby A. S., aged 23 months, male, was admitted to the Bryn Mawr Hospital on May 31 on the service of Dr. Longaker with diagnosis of acute bilateral mastoiditis, for which he was operated upon. The child had septic temperature with rise to 105.5° F. Two blood cultures showed *S. hemolyticus* in very large number, the child later developing extensive cellulitis of the arm and leg. On June 3 patient had a leukocyte count of 7100 of which only 1633 cells were mature polys. The baby received 5 leukocytic cream injections. Within 24 hours from the first injection the blood examination showed a total leukocyte count of 9500 with 3800 mature polys; 4 days after the first injection the total leukocyte count was 15,000 with 5250 mature neutrophils. In view of the fact that in cases of this sort the fluctuation of the total cell count as well as of the mature neutrophils is often great, it is not possible to state what effect the leukocytic cream injection had, inasmuch as only the examination of numerous cases might decide the question. In this case the hematologic improvement was paralleled by a slight but definite clinical improvement.

Leukocytic cream injections in adequate amounts have been so far tried in 3 normal patients carefully studied. None of them appeared to show any increase of granulocytes or an increase of the young forms above what might be considered the physiologic fluctuations.

It is too early to attempt to form a theory in regard to the mechanism of the action of leukocytic cream injections, if any. I venture, however, to say that because of the short interval of time between the injections and the hematologic response in all probability we are dealing with a phenomenon of maturation more than multiplication of cells. It is also possible that the release of already mature cells is affected, although this seems to be less likely.

Conclusions. Evidence is presented that injections of leukocytic cream intramuscularly in severe neutropenias is followed in most cases within 1 to 4 days, usually 48 hours, by an increase of mature granulocytic cells in circulation, along with a considerable clinical improvement.

A method for preparation of the leukocytic cream is given.

BIBLIOGRAPHY.

1. Vaughan, V. C., Novy, F. G., and McClintock, C. T.: Med. News, 1893, **62**, 536.
2. Ames, D., and Huntley, A. A.: J. Am. Med. Assn., 1897, **29**, 472.
3. De Paoli, E., and Calisti, A.: Mitt. a. d. Grengeb. d. Med. u. Chir., 1912, **24**, 275.
4. Doan, C. A.: J. Am. Med. Assn., 1932, **99**, 194.
5. Sabin, F. R.: Bull. Johns Hopkins Hosp., 1923, **34**, 277.
6. Sabin, F. R., Cunningham, R. S., Doan, C. A., and Kindwall, J. A.: Ibid. 1925, **37**, 14.
7. Doan, C. A., and Zerfas, L. G.: J. Exp. Med. 1927, **46**, 511
8. Jackson, H., Jr., Parker, F., Jr., Rinehart, J. F., and Taylor, F. H. L.: J. Am. Med. Assn., 1931, **97**, 1436.
9. Jackson, H., Jr., Parker, F., Jr., and Taylor, F. H. L.: AM. J. MED. SCI., 1932, **184**, 297.
10. Dameshek, W., and Ingall, M.: Ibid., 1931, **181**, 502.
11. Fitz-Hugh, T., Jr., and Comroe, B. I.: Ibid., 1933, **185**, 552.

THE EFFECT OF HYPERPYREXIA INDUCED BY RADIATION UPON THE LEUKOCYTE COUNT.

By William Bierman, M.D.,
DIRECTOR, DEPARTMENT OF PHYSICAL THERAPY, BETH ISRAEL AND SYDENHAM HOSPITALS; INSTRUCTOR, DEPARTMENT OF SURGERY (PHYSICAL THERAPY), COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK.

(From the Department of Physical Therapy, Beth Israel Hospital.)

Various methods are now available which permit controlled elevation of the temperature of the human body by means of physical energy. This affords opportunity of studying the physiologic changes occurring in the body as a result of such temperature elevation apart from infections. In fever produced endogenously by invading microörganisms, or the injection of foreign proteins or toxic substances, it is not possible to separate the thermal from the other factors. We observed changes occurring in the leukocyte count during hyperpyrexia produced in the human subject as a result of exposure to radiations of a wave length of about 30 m. In most instances the temperature as determined by rectal thermometer was raised to 104° to 106° F. and maintained for 3 to 4 hours by surrounding the patient with a hood containing some carbon filament lamps.

Our study included 39 determinations in 24 cases, suffering from the following diseases: chronic arthritis, 6 cases; gonorrheal arthritis, 3; central nervous system lues, 5; multiple sclerosis, 2; and 1 case each of encephalitis, basal ganglion disease, pelvic inflammatory disease, sympathetic ophthalmia, sciatic scoliosis, and carcinoma of the stomach. On several occasions, counts were taken on the morning and sometimes on the afternoon of the following day. The blood was usually taken from the finger tip. Smears were stained with the Jenner-Giemsa and Wright solutions. Hemoglobin determinations were made by means of the Sahli technique. The varieties of the white blood cells were grouped into the staff neutrophils, the total neutrophils, the monocytes and lymphocytes.

Results. The initial reaction was a reduction in the number of white blood cells. This was usually seen at the end of the first or second hour after the beginning of the treatment. In 6 instances this initial diminution in the number of white blood cells was not observed. It is possible that the failure to make this observation was due to the fact that the first blood count following the start of the treatment was not made soon enough. In most instances the reduction in the number of white blood cells amounted to from 25 to 30 per cent (limits, 2 and 40 per cent).

By the 3d, 4th or 5th hour after the onset of treatment, the

number of white blood cells had risen to a level above the initial figure. The peak of the leukocyte count usually occurred at the 6th to the 9th hour. The increase in the number of the white blood cells averaged about 50 per cent in those instances where the count was followed for a period of about 6 to 8 hours. It averaged about 80 per cent where the count was followed to its highest point. At times this increase amounted to more than 100 per cent. In only 2 instances did we fail to observe an increase in the number of the white blood cells. The leukocyte count rose as high as 22,600. Immature forms such as myelocytes, metamyelocytes, premyelocytes, and myeloblasts were seen.

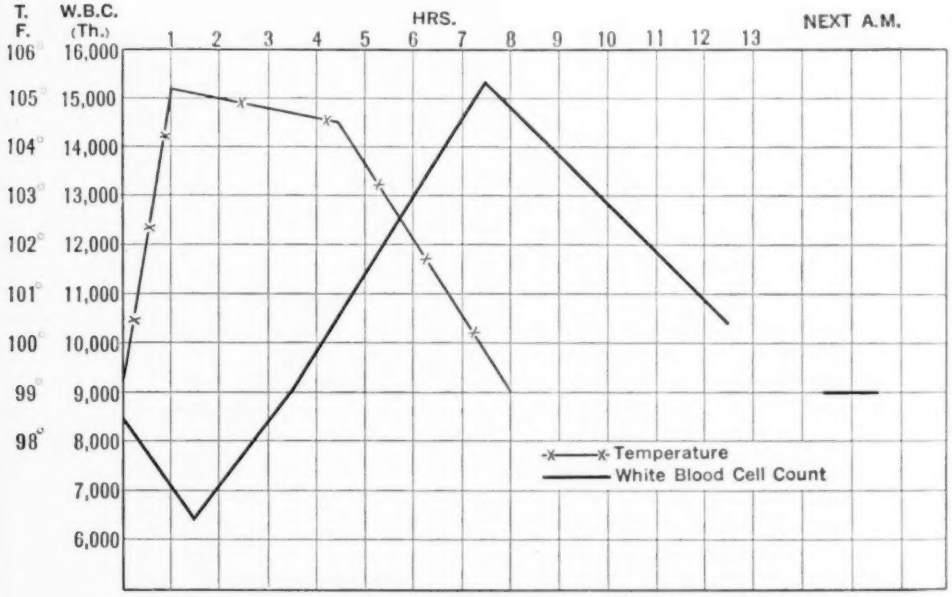


FIG. 1.—Composite graph showing relationship between temperature elevation and the leukocyte count.

The greatest percentage of increase was seen in the staff cell count. This increase averaged about 300 per cent and was about 200 to 300 per cent in most instances, on one occasion rising to 1420 per cent. The peak of the staff cell count usually occurred at about the 9th hour. In about $\frac{1}{3}$ of the observations the rise in the number of staff cells was preceded by a fall, usually occurring at the end of the 1st or 2d hour, and which, in the majority of cases, amounted to about 30 per cent. The swing of the staff cell count coincided more or less with that of the total neutrophils.

The total number of the neutrophils showed an average diminution of about 25 per cent, occurring usually at the 1st, 2d or 3d hour.

If the count was followed long enough, the maximum rise was seen to occur from the 5th to the 9th hour. The average increase was about 140 per cent.

In about ½ of the instances there was a diminution in the number of monocytes, which averaged about 45 per cent. The low point of the fall usually occurred at the 1st, 2d or 3d hour; the high point, from the 5th to the 14th hour. The average percentage of increase was about 270.

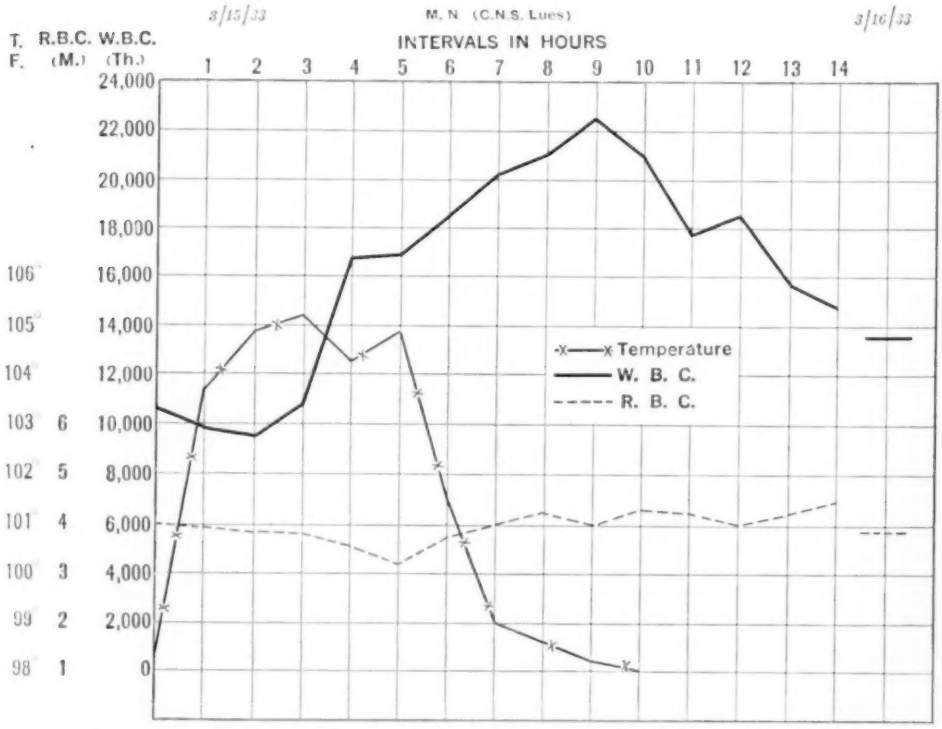


FIG. 2.—A case representing the relationship between systemic temperature, leukocyte and erthrocyte levels.

The average reduction in the number of lymphocytes amounted to about 40 per cent. The smallest numbers were observed at the 3d or 4th hour. In about ½ of the instances the lymphocyte count had not returned to its original figure when blood counts were made for a period of only 6 to 8 hours. In the other ½ the average rise was about 35 per cent. When the counts were observed for 13 to 14 hours, it was noticed that the time of the height of the rise occurred from the 6th to the 11th hour and the increase averaged about 90 per cent.

In general, the white blood cells from the bone marrow first showed the stimulating influence of the hyperpyrexia—the segmented neutrophils and the staff neutrophils. The monocytes, whose origin

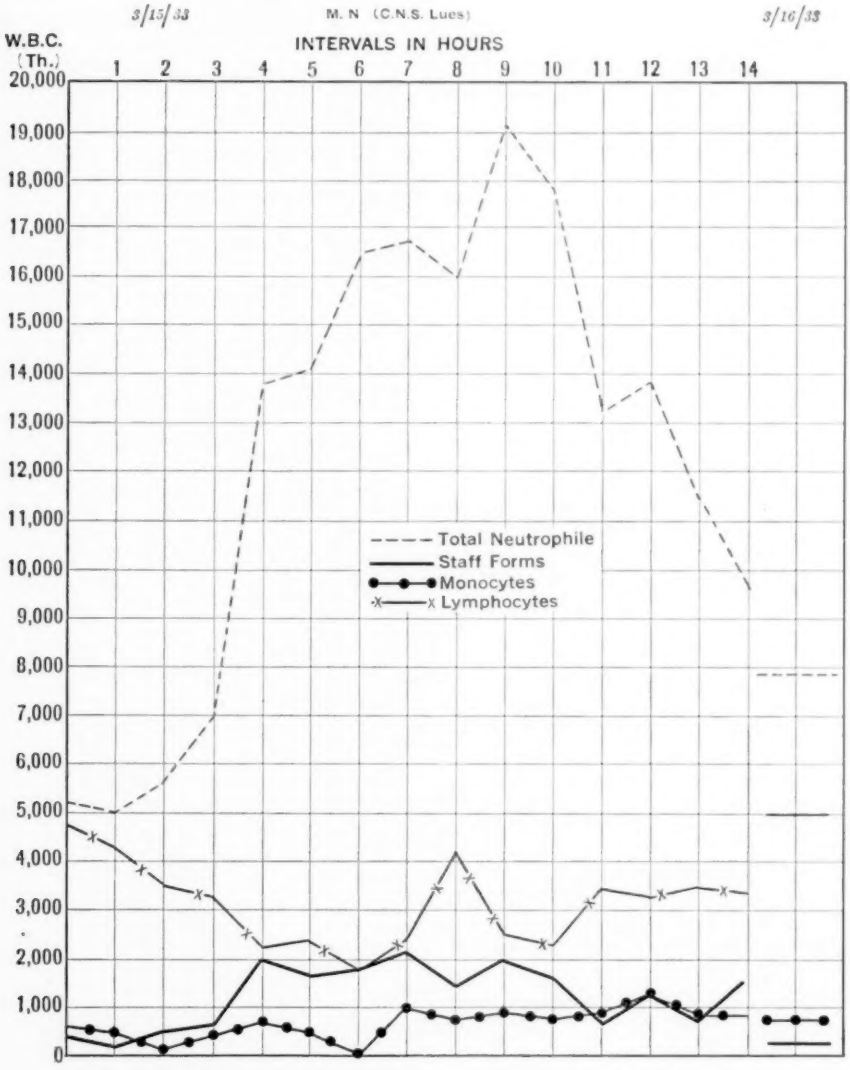


FIG. 3.—The differential count of the leukocyte response indicated in Fig. 2.

is ascribed to the reticuloendothelial system[1] are the next to give evidence of an increase in their number, and, last, those from the lymphatic system—the lymphocytes.

When the hyperpyrexia treatments were administered at frequent

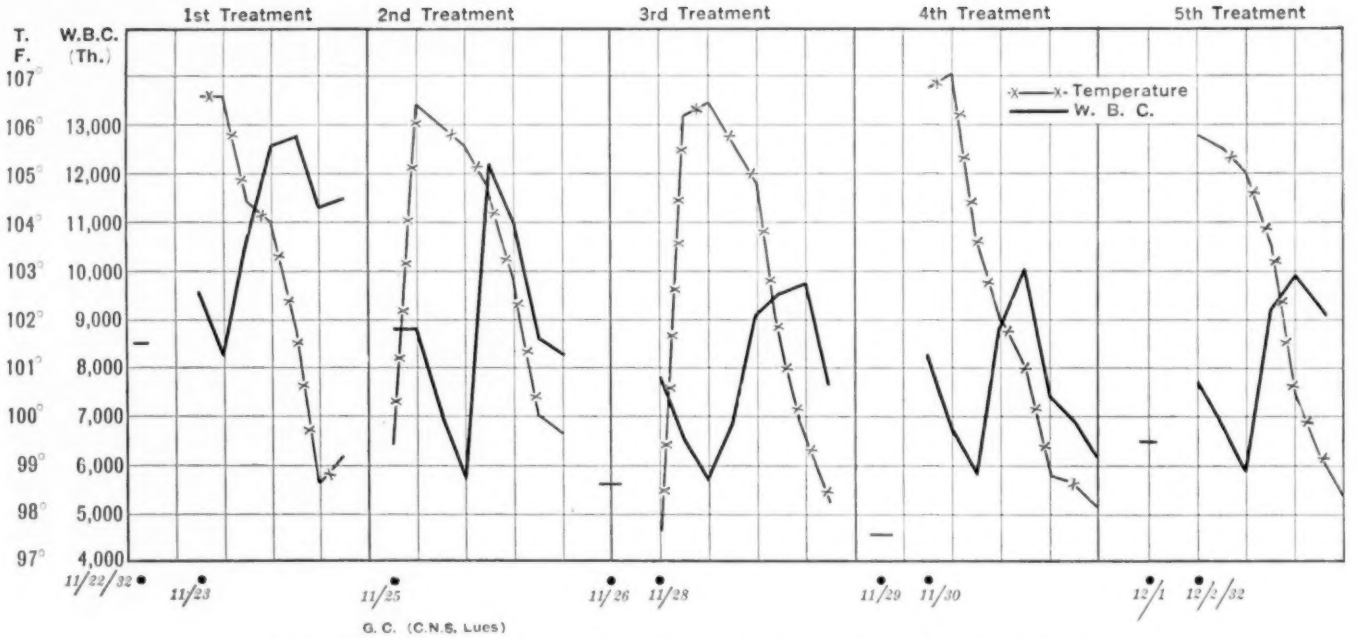


FIG. 4.—Effect of frequently repeated hyperpyrexia treatments upon the leukocyte count.

intervals, *e. g.*, every other day, the leukocytic response became diminished and the number of the white blood cells on the days between treatments became lower.

Comments. From these observations it will be noted that the characteristic change in the number of white blood cells occurring during electrically induced hyperpyrexia is an initial fall followed by a rise in the number of the leukocytes. This swing took place in nearly all of the cases studied. It occurs even when there has already been a retardation of the mechanism which is responsible for a diminished number of white blood cells in the peripheral circulation (as in a case of carcinoma of the stomach exposed to high-voltage Roentgen ray radiations and showing a severe leukopenia).

Three to 5 hours elapse before the stimulating influence of the hyperpyrexia upon the hematopoietic system becomes evident in the peripheral circulation, as determined by the enumeration of the white blood cells and the appearance of immature forms.

It should be of interest to the clinician to observe that the maximum leukocytosis may occur at a time when the temperature has returned to the normal level. This may explain the finding of an increased number of white blood cells in a patient who may have had an elevation of temperature a few hours preceding the taking of the count.

A leukocytosis occurs even though the temperature be only slightly elevated and maintained for a short period of time. The height of the leukocyte rise appears to depend not only upon the height to which the temperature is raised, but also upon the length of time during which the temperature elevation persists.

The change in the number of white blood cells cannot be explained on the basis of a change in the blood volume. The percentage of hemoglobin and the number of red blood cells does not show a fluctuation at all comparable to that occurring in the number of white blood cells. These patients may lose as much as 2 to 3 liters of fluid (mainly through the sweat). This may be balanced, however, by the fluid intake if the patient is permitted to drink all the fluid he desires. Also, the increase of immature cells could not be explained in this way.

Leukocytosis has been shown to occur after the injection of malarial plasmodia[2] and typhoid vaccine.[3] In both of these instances a marked elevation of body temperature occurs.

According to Mueller, the fall in the number of white blood cells occurring during the initial stage of temperature elevation can be explained on the basis of an overbalance of the sympathetic nerves. "The liver and the vessels of the splanchnic region show a contrary fixation when the parasympathetic vasodilating nerves prevail. The splanchnic region, as represented in one part by the liver, and the periphery, as represented in one part by the skin, form 2 large sys-

tems balancing each other as far as the nervous control is concerned and holding in balance also the number of leukocytes in their vessels."[4] While this may be a possible explanation for the initial changes observed during hyperpyrexia, we have no evidence indicating capillary contraction. Unlike the condition noted during the period of chill following intravenous injection of typhoid vaccine, the skin surface during the administration of electrically induced hyperpyrexia is warm, its temperature begins to rise, and sweating usually occurs within a few minutes.

The subsequent leukocytosis must be due to stimulation of the hematopoietic system as evidenced by the occurrence of immature forms such as myelocytes, metamyelocytes, premyelocytes, and myeloblasts. Jacobsen and Hosoi, in discussing the morphologic changes occurring in tissues as a result of the development of high temperature produced by means of the electric current, describe a congestion of the organs and evidence of the stimulation of the bone marrow.[5]

The changes in the number of white blood cells after typhoid vaccine injection and induced malaria have shown an initial diminution followed by a leukocytosis similar to ours. Leukocyte counts as high as 62,000 per cu.mm. have been reported after the injection of typhoid vaccine intravenously.[7] Our highest count has been 22,600.

Weiss[2] has described blood changes occurring during the paroxysm of malarial fever as consisting of a rise, first, in the number of neutrophils, followed by an increase in the number of monocytes and then by an increase in the number of lymphocytes. This corresponds to the changes we have observed. Schilling has described these as phases of struggle, defense or subjection, and healing.[1]

The diminution of the leukocytic response after repeated hyperpyrexia treatments with the lowering of the white blood cell count on the days between treatments would indicate a lessening of the hematopoietic system's reaction to the stimulating influence of heat. Similarly, it has been observed that after repeated intravenous injections of typhoid vaccine, the leukocytic reaction becomes less marked.[7] This diminution of the leukocytic response has also been noted to occur following the repeated administration of radiothermy treatments for general paralysis.[8]

Conclusions. Hourly observations were made of the changes occurring in the leukocyte count of patients suffering from varied diseases in whom hyperpyrexia was induced by means of radio waves of 30-meter length.

An initial reduction, about 25 to 30 per cent, in the number of leukocytes regularly occurs, usually during the 1st or 2d hour of treatment. This is constantly followed by a leukocytosis whose maximum, amounting to about 80 per cent above the initial figure, occurs about the 6th to the 9th hour.

These variations are due mainly to changes in the total number of neutrophils, of which the staff neutrophils show the greatest increase. These changes, together with the appearance of other immature forms, indicate a stimulation of the bone marrow.

At a later stage the monocytes and lymphocytes also increase in number.

Repeated stimulation by heat is followed by a reduction in the leukocytic response.

I desire to express my thanks to Dr. Willys R. Whitney, of the General Electric Company, for placing a short-wave radiation machine at my disposal, and to Miss Janet Greenberg and Miss Rosalie Koplik for their technical assistance.

REFERENCES.

1. Schilling, V.: The Blood Picture, St. Louis, The C. V. Mosby Company, 1929.
2. Weiss, A.: Ztschr. f. klin. Med., 1926, **103**, 427.
3. Cowie, D. M., and Calhoun, H.: Arch. Int. Med., 1919, **22**, 69.
4. Mueller, E. F.: Ibid., 1926, **37**, 268.
5. Jacobsen, V. C., and Hosoi, K.: Arch. Path., 1931, **2**, 744.
6. Bunker, H. A., Jr.: Am. J. Med. Sci., 1926, **172**, 681.
7. Scully, F. T.: J. Am. Med. Assn., 1917, **69**, 20.
8. Hinsie, L. E., and Blalock, J. R.: Psychiat. Quart., 1931, **5**, 432.

THE RELATIONSHIP BETWEEN THE ERYTHROCYTE SEDIMENTATION RATE AND THE FIBRINOGEN CONTENT OF PLASMA.

By D. Rourke Gilligan, M.S.,
Research Fellow in Medicine, Harvard Medical School,
and
A. Carlton Ernstene, M.D.,
Instructor in Medicine, Harvard Medical School,
Boston, Mass.

(From the Medical Research Laboratories and the Medical Service of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.)

During recent years the rate of erythrocyte sedimentation has been shown to be influenced by many factors. It has been demonstrated[12,14] that to obtain a reliable sedimentation-rate measurement, venous stasis should be avoided in collecting the blood, heparin should be used as the anticoagulant, the blood should not stand more than 3 hours before the test is started, and the room temperature should remain between 20° and 25° C. during the measurement. Further the rate of settling bears an inverse ratio to the volume percentage of red blood cells;*[4,5,12] the fewer the red blood cells in a specimen of blood, the faster the sedimentation rate. In a previous

* For the purpose of brevity, here and elsewhere in this note complete references are not given. The bibliographies of two reviews (References 4 and 8) are referred to repeatedly.

communication[12] a method was reported by means of which the sedimentation rate for any specimen of blood can be corrected to the rate which would have been obtained if the sample of blood had contained 45 volumes per cent of cells. The rate thus obtained was termed "the corrected sedimentation index." This method,[12] which embodies all the precautions enumerated by Rourke and Plass[14] and also corrects for variations in cell volume percentage of the blood, appears to us more suitable for further correlation of the erythrocyte sedimentation rate with accompanying chemical or physical changes in the blood plasma than other methods in clinical use.

Several investigators have reported varying degrees of correlation between increased fibrinogen content of the plasma and increased rate of erythrocyte sedimentation.[2,3,4,6,7,10] It has been observed, in addition, that when the fibrinogen content of the plasma is reduced by administering chloroform to the dog, the erythrocyte sedimentation rate is diminished in proportion to the decrease in plasma fibrinogen content.[13] In only one of the above mentioned studies[2] was the sedimentation rate corrected for variations in the cell volume percentage of the blood, and here a close correlation was observed between the corrected sedimentation index and the plasma fibrinogen content in patients with rheumatic fever.

Simultaneous measurements of the corrected sedimentation index and plasma fibrinogen content have been made in this laboratory in a large number of normal individuals and in patients with various pathologic conditions. It seemed desirable to assemble this data to determine the correlation between the plasma fibrinogen content and the corrected sedimentation index.

Results and Discussion. In Fig. 1 the fibrinogen content of the plasma, measured as fibrin by the method of Wu,[16] has been charted against the corrected sedimentation index in 190 instances. The diagnoses in the subjects on whom observations were made are presented in Table 1: 39 clinical conditions are represented. Not more than four points have been charted from measurements on any individual during the course of his disease. The normal area (Fig. 1) for fibrinogen content and corrected sedimentation index has been blocked out between the limits of 0.22 to 0.32 gm. per cent fibrinogen, and 0.08 to 0.35 mm. per minute corrected sedimentation index. These limits are based on observations made in this laboratory in a large series of normal individuals. The open dots at the extreme top of the chart represent sedimentation rates so rapid that the corrected sedimentation indices had to be interpolated above the upper line on the correction chart presented in the paper describing the method.[12] The manner in which this interpolation is made is described in the same communication. The crosses in Fig. 1 represent the results of 6 tests on 5 patients who had acute hepatitis at the time of the test or who had in the past been hospitalized for acute hepatitis.

The degree of correlation, shown graphically in Fig. 1, indicates a close relationship between the plasma fibrinogen content and the corrected sedimentation index. It has been established that the fibrinogen content of the plasma as well as the rate of erythrocyte sedimentation is increased in infectious diseases.[8] Plass and Matthew[11] demonstrated that the plasma fibrinogen content in-

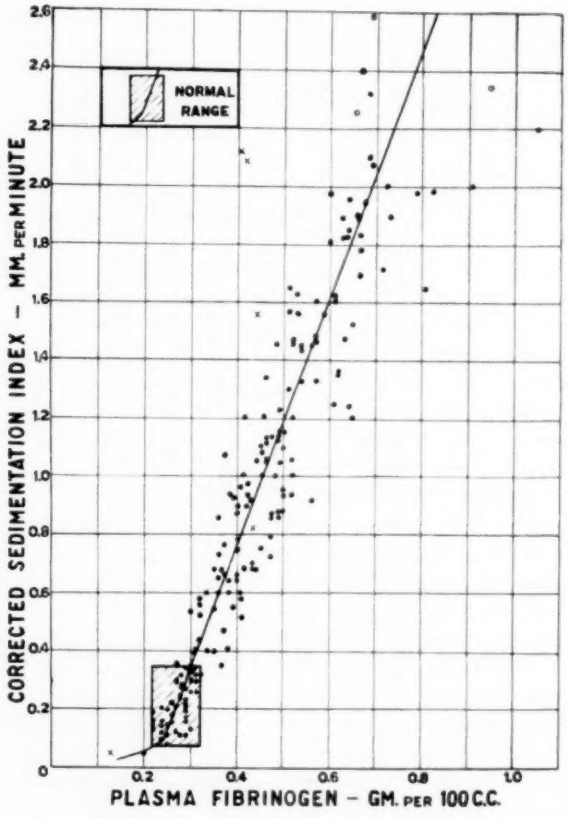


FIG. 1.—The relationship between the corrected sedimentation index and the fibrinogen content of the plasma in 190 instances, representing 39 different clinical diagnoses.

creases gradually during pregnancy and that there is a close relationship between the average fibrinogen values during the different months of pregnancy and the average sedimentation rates reported by Linzenmeier[9] for the same periods.

Because the plasma globulin content frequently is increased in the presence of infection,[4,8] several investigators have believed that increased sedimentation rates depend to a large extent on increased

concentration of plasma globulin. Plass and Matthew[11] observed, however, that the plasma globulin remains practically constant during pregnancy, and they believe that the increased fibrinogen content of the plasma plays the major rôle in the progressively increased sedimentation rate during the course of pregnancy. Furthermore, if blood from a patient with severe infection is defibrinated the rate of settling of the erythrocytes is almost negligible as compared to the rapid rate of settling of a non-defibrinated sample of the same blood.[1,4]

TABLE 1.—SUBJECTS STUDIED.

Diagnosis.	No. of tests.	Diagnosis.	No. of tests.
Normal	40	Syringomyelia	1
Lobar pneumonia	10	Multiple sclerosis	1
Bronchopneumonia	4	Carcinoma at head of pancreas, jaundice	1
Rheumatic fever, acute	19	Abdominal carcinoma, site undetermined, ascites	1
Infection, acute respiratory	4	Carcinoma of sigmoid	4
Abscess of lung	1	Osteosarcoma of ilium	1
Injection abscess, syphilis	1	Cholecystitis, chronic	1
Pulmonary tuberculosis, active	2	Ulcer of duodenum	1
Fever (cause unknown)	1	Rheumatic heart disease, compensated	1
Multiple carbuncles	1	Myxedema	1
Empyema of pleura	1	Exophthalmic goiter	7
Influenza	1	Osteogenesis imperfecta	1
Arthritis, gonorrheal	1	Herniorrhaphy	27
Arthritis, infectious	12	Common bile duct obstruction	1
Hepatitis, acute	6	Amputation	3
Coronary thrombosis	1	Appendectomy and removal of ovarian cyst	1
Hodgkin's disease	2	Ligation of Fallopian tubes	1
Pansinusitis, acute	1	Arsphenamin dermatitis, syphilis	1
Appendicitis, acute and appendectomy	18		
Post-encephalitic paralysis agitans	2		
Tumor of brain	2		

The results obtained in 3 patients with acute hepatitis (Fig. 1) show essentially the same correlation between the plasma fibrinogen content and the corrected sedimentation index as was found for the other clinical conditions studied. In 1 of these patients the test was made shortly before death and showed both the plasma fibrinogen content and the corrected sedimentation index reduced below the normal limits (Fig. 1); in the other 2 patients the tests were made early in the illness. In 2 additional patients the tests were made after recovery from acute hepatitis and the corrected sedimentation index was observed to be increased disproportionately to the increase in the plasma fibrinogen (Fig. 1, indices 1.56, 2.08 and 2.12, indicated by crosses). The results in these 2 patients are in harmony with the findings of Bendien and Snapper[1] who reported increased sedimentation rates (Westergren's method[15]) in the presence of normal plasma fibrinogen values in certain cases of cirrhosis of the liver. These investigators found that the rate of settling of the erythrocytes of the defibrinated blood from these patients with cirrhosis of the liver was much more rapid than the rate of

settling of the erythrocytes of the defibrinated blood from patients with no liver involvement. The results of Bendien and Snapper and the observations above suggest, therefore, that the increase in the sedimentation rate found in these special cases is due in part to factors other than the fibrinogen content of the plasma.

That the plasma globulin and albumin content, the concentration of other colloids and crystalloids, and the plasma viscosity have some effect on the erythrocyte sedimentation rate is well recognized. The degree of correlation obtained between the fibrinogen content of the plasma and the corrected sedimentation index (Fig. 1) indicates, however, that the plasma fibrinogen content is the major factor which determines the corrected sedimentation index in the majority of cases. The explanation for this relationship must rest on the physicochemical properties of the plasma fibrinogen in respect to its effect on red cell aggregation;[4] the greater the plasma fibrinogen content, the greater the size of the settling red cell aggregates with a consequent greater speed of erythrocyte sedimentation.

Summary. 1. One hundred and ninety simultaneous measurements of the fibrinogen content of the plasma and the "corrected sedimentation index" were made in normal individuals and in patients with various kinds and degrees of pathologic conditions.

2. A close correlation was observed between the plasma fibrinogen content and the corrected sedimentation index.

3. In certain cases with liver damage the corrected sedimentation index is increased disproportionately to the increase in plasma fibrogen content.

4. The results of the investigation indicate that, except in certain cases with liver damage, the plasma fibrinogen content plays the major rôle in controlling the corrected sedimentation index.

REFERENCES.

1. Bendien, W. M., and Snapper, I.: Biochem. Ztschr., 1931, **235**, 14.
2. Ernstene, A. C.: Am. J. Med. Sci., 1930, **180**, 12.
3. Fahraeus, R.: Acta med. Scand., 1921, **55**, 3.
4. Fahraeus, R.: Physiol. Rev., 1929, **9**, 241.
5. Gram, H. C.: Acta med. Scand., 1928, **68**, 108.
6. Greisheimer, E. M., Johnson, O. H., and Ryan, M.: Am. J. Med. Sci., 1929, **177**, 816.
7. Greisheimer, E. M., Worwick, M., and Walton, M.: Am. J. Dis. Child., 1929, **37**, 953.
8. Howe, P. E.: Physiol. Rev., 1925, **5**, 439.
9. Linzenmeier, G.: Arch. f. Gynäk., 1920, **93**, 608.
10. Moen, J. K., and Reimann, H. A.: J. Clin. Invest., 1933, **12**, 589.
11. Plass, E. D., and Matthew, C. W.: Am. J. Obst. and Gynec., 1926, **12**, 3.
12. Rourke, M. D., and Ernstene, A. C.: J. Clin. Invest., 1930, **8**, 545.
13. Rourke, M. D., and Plass, E. D.: Am. J. Physiol., 1928, **84**, 42.
14. Rourke, M. D., and Plass, E. D.: J. Clin. Invest., 1929, **7**, 365.
15. Westergren, A.: Acta med. Scand., 1920–1921, **54**, 247.
16. Wu, H.: J. Biol. Chem., 1922, **51**, 33.

VITAMIN THERAPY IN PULMONARY TUBERCULOSIS.

V. THE EFFECT OF VIOSTEROL ON THE DIFFUSIBLE AND NON-DIFFUSIBLE CALCIUM OF THE BLOOD AND SPINAL FLUID.

BY PAUL D. CRIMM, M.D.,
MEDICAL DIRECTOR,
AND
J. W. STRAYER, M.D.,
RESIDENT PHYSICIAN, BOEHNE TUBERCULOSIS HOSPITAL,
EVANSVILLE, INDIANA.

IT is the consensus of opinion that cerebrospinal fluid is that part of the blood which diffuses through the capillary walls and endothelial membranes of the choroid plexus. Thus it represents the diffusible fraction of calcium in the blood. Several investigators have used semipermeable membranes for testing the diffusibility of calcium *in vitro*. Their results have varied with the differences in the permeability of the respective membranes.

Methods. Serum and spinal fluid calcium was determined by the Clark and Collip[1] method, modification of Kramer and Tisdall.[2] Phosphorus determinations were made by the method of Benedict and Theis.[3] The serum and spinal fluid were obtained simultaneously at the same time of day. Determinations were performed immediately.

Historical Data. The results of numerous investigators (4 to 23) are compiled in Table 1.

In 20 normal cases we found the spinal fluid calcium to be 5.7 mg. per 100 cc., while in the same series the serum calcium averaged 11.1 mg. In 25 cases of pulmonary tuberculosis we found the spinal fluid calcium to be 6.2 mg. and the serum calcium to be 11.2 mg. In the same series of normal individuals, the serum phosphorus averaged 4.2 mg. and the spinal fluid phosphorus 1.9 mg. per 100 cc. The same values for phosphorus were found in the blood and spinal fluid in the 25 cases of pulmonary tuberculosis. In 41 normal individuals Cohen[24] found the phosphorus range in the spinal fluid to be 1.25 to 1.90 mg., with an average of 1.64 mg. per 100 cc.

Diffusible Calcium. Viosterol increases the absorption and retention of calcium.[25] Serum calcium is one of the indices of this physiological mechanism. The question arises as to whether viosterol increases the diffusible or the non-diffusible calcium. Agreeing with Cameron and Moorhouse,[17] we use the preceding terms rather than the terms "ionized" and "ionic" calcium as used by Vines.[26] According to them diffusible calcium is that fraction which includes calcium ions and unionized inorganic calcium compounds which can diffuse through a normally functioning animal membrane.

Rona and Takahashi[27] found that 65 to 75 per cent of the serum calcium of the horse, pig and cow is dialyzable with membranes;

TABLE 1.—COMPARISON OF SERUM CALCIUM WITH SPINAL FLUID CALCIUM IN NORMALS AND IN PATHOLOGIC CASES.

No. of cases.	Examiner.	Type of case.	Mg. per 100 cc.	
			Serum calcium.	Spinal fluid calcium.
20	Mestrezat	Normals	....	7.1
4	Kummer and Minkoff	Normals	....	5.0-5.2
12	Leicher	Normals	11.4	5.0
..	Depisch and Richter-Quittner	Normals	....	2.5
3	Pincus and Kramer	Normals	10.5	4.8
38	Critchley and O'Flynn	Normals	....	6.1
59	Neustaedter, *et al.*	Normals	....	5.8
68	Cantarow	Normals	9.2-11.0	4.5-5.5
20	Crimm and Strayer	Normals	11.1	5.7
	Normal average		10.8	5.2
2	Schmidt	Hydrocephalus (Adult)	....	15.3
		(Fetus)	....	7.0
1	Yvon	(Fetus)	....	8.0
1	Mestrezat	" (After death)	....	6.2
25	Halverson and Bergeim	Various diseases	....	5.1
1	Halverson and Bergeim	Paralytic dementia	....	6.0
12	Mann	Epileptics	....	8.0-9.0
6	Mann	Non-epileptics		
27	Weston Howard	Manic- Depr. Insanity		
		(Excited)	....	5.2
		(Depressed)	....	5.4
..	Leicher	Intracranial pressure (various)	....	4.7-5.7
..	Barrio	Cerebrosp. syph.	....	4.6-6.1
77	Critchley and O'Flynn	Pathologic	....	5.2-8.0
20	Cameron and Moorhouse	*Dogs. Normal	11.1	5.8
17	Nourse, Smith and Hartman	Spasmophilia (following cure)	9.9	4.8
17	Hamilton	Epilepsy	9.6-12.8	4.4-6.6
9	Merritt and Bauer	Pul. tuberc.	9.0	4.6
22	Cooper	Pul. tuberc.	10.4	4.8
18	Booth and Broga	Pul. tuberc.	9.4-16.3	5.2-7.6
25	Crimm and Strayer	Pul. tuberc.	11.2	6.2
	Pathologic average		10.7	6.4

* Not included in average

von Meysenbug, Pappenheimer, Zucker and Murray[28] obtained 60 to 70 per cent for normal men and dogs; Cruikshank,[29] 55 to 70 per cent in dogs. Loeb[30] found 55 to 75 per cent calcium diffusible against distilled water, and a pH of 7.4; Tischimber,[31] 50 to 60 per cent; Cushny,[32] by ultrafiltration obtained 62 to 70 per cent. Moritz[33] found the diffusible fraction of serum calcium in rabbits to average 56 per cent although Updegraff, Greenberg and Clark[34] cor-

rected his data to average 68 per cent. Lui[35] obtained values ranging from 42.5 to 48 per cent of the total serum calcium. Neuhausen and Pincus[36] found that 50 to 75 per cent of pig serum calcium is diffusible.

Vines[26] concluded that diffusible calcium is about 63 per cent of the plasma calcium. Cameron and Moorhouse[17] stated that the average true diffusible calcium of blood plasma in normal dogs was 53 per cent of the serum calcium value. Cantarow[23] found the diffused calcium to be about 45 to 55 per cent of the total calcium.

In a series of 20 normal individuals we found that the diffusible calcium represented 51 per cent of the total serum calcium. In 25 cases of pulmonary tuberculosis, the majority being of an exudative type, the diffusible calcium averaged 55 per cent of the serum calcium. Booth and Broga[22] and Cantarow[23] found an increased diffusibility ratio in this type of pulmonary tuberculosis, that is, ratio of diffusible to non-diffusible calcium.

The Diffusibility Ratio. Table 2 presents an analysis of 10 cases of pulmonary tuberculosis. Specimens for the determinations were taken at the same time of the day. The average serum calcium was 11.1 mg., while the spinal fluid calcium was 6.1 mg. per 100 cc. Phosphorus in the serum was 4.6 mg., while the phosphorus in the spinal fluid was 2.1 mg. per 100 cc. The diffusibility ratio for the 10 cases averaged 127 per cent. Five of the cases which had a serum calcium value of 11.7, 10.8, 12.1, 12.4 and 11.8 mg. per 100 cc. respectively, were chronically ill. The other 5 cases were acutely ill. None of the cases presented symptoms of intestinal tuberculosis. The 5 subjects who were chronically ill had an average diffusibility ratio of 90 per cent, while the 5 acutely ill averaged 165 per cent.

TABLE 2.—THE BLOOD SERUM AND SPINAL FLUID CALCIUM OF TEN CASES OF PULMONARY TUBERCULOSIS.

Case No.	Blood serum.				Spinal fluid.				D/ND ratio.†	
	Before viosterol.		After viosterol.		Before viosterol.		After viosterol.		Before viosterol.	After viosterol.
	Ca.*	P.*	Ca.*	P.*	Ca.*	P.*	Ca.*	P.*		
1156	10.9	4.9	13.3	4.6	7.6	2.0	7.1	2.9	230	114
1146	10.6	5.5	16.3	6.6	6.2	2.9	6.8	2.8	140	71
1140	9.4	4.4	15.4	5.6	6.0	2.3	6.6	2.3	176	75
1134	11.7	4.8	15.5	5.0	5.5	2.4	6.4	2.6	88	70
1130	10.8	4.4	16.6	5.6	5.2	1.8	7.2	2.0	93	76
1115	12.6	4.4	15.0	4.3	6.5	2.0	6.6	2.3	106	78
1012	12.1	4.7	17.1	5.2	5.3	1.9	7.3	1.7	78	74
1109	12.4	5.3	15.4	5.6	5.9	1.9	8.4	2.0	90	120
614	10.9	4.5	13.3	4.3	6.9	2.3	8.4	2.6	172	171
966	11.8	3.4	14.0	4.2	5.9	1.8	7.6	2.5	100	118
Average	11.1	4.6	15.1	5.2	6.1	2.1	7.2	2.4	127	96

* Values expressed as milligrams per 100 cc. of serum or fluid.
† Ratio of diffusible to non-diffusible calcium expressed as percentage.

In the series of 25 cases of pulmonary tuberculosis, the diffusibility ratio averaged 139 per cent with a range of 82 to 315 per cent. In the 20 normal individuals previously mentioned the diffusibility ratio averaged 104 per cent with a range of 82 to 160 per cent.

In 63 cases of pulmonary tuberculosis, Cantarow[23] found the diffusibility ratio to range from 56.7 to 152 per cent. Cooper[21] in 10 cases of pulmonary tuberculosis, exudative type, reported a diffusibility ratio of 88 per cent and in 12 cases of the productive type a diffusibility ratio of 87 per cent. Booth and Broga[22] determined in 18 cases of pulmonary tuberculosis a diffusibility ratio of 50 to 158 per cent. In the 11 cases of pulmonary tuberculosis, proliferative type, studied by Cantarow,[23] the diffusibility ratio was below 100 per cent in 9 of the cases; the decrease in the diffusibility ratio was attributed to a primary increase in non-diffusible calcium.

The Effect of Viosterol on the Diffusible and the Non-diffusible Calcium. In our series of 25 cases, 1, fibroid type, had a diffusibility ratio of 315 per cent. This was due to a decrease in non-diffusible calcium, the serum calcium being 8.3 mg. and the spinal fluid calcium 6.3 mg. per 100 cc. This patient received viosterol 250 D,* 1.5 cc. (60 gtts.) q. d. for 4 weeks. At the end of this viosterol period the diffusibility ratio had decreased from 315 to 102 per cent, due to an adequate absorption of calcium.

Another case, fibroid type with chronic bronchitis, had a diffusibility ratio of 236 per cent, due to a high diffusible calcium content, the serum calcium being 11.1 mg. and the spinal fluid being 7.8 mg. per 100 cc. For a period of 3 weeks, viosterol 10,000 X †, 0.5 cc. (20 gtts.) q. d., reduced the diffusibility ratio from 236 to 93 per cent. After viosterol was discontinued an increase in the non-diffusible calcium was accompanied by a decrease in the diffusible calcium. It is advisable to use 250 D to accomplish this result. Most cases do not tolerate 10,000 X for a longer period than 8 days.

In 10 cases of pulmonary tuberculosis (Table 2), the normal calcium averaged 11.1 mg. and the phosphorus 4.6 mg. per 100 cc. Following the administration of viosterol 10,000 X the average serum calcium rose to 15.1 mg. and the phosphorus to 5.2 mg. per 100 cc. The spinal fluid calcium was determined at the same time and the diffusible calcium for this series averaged 6.1 mg. and the phosphorus 2.1 mg. per 100 cc. After the administration of viosterol 10,000 X, the calcium rose to 7.2 mg. and the phosphorus to 2.4 mg. per 100 cc. Diffusible calcium represented 55 per cent of the total calcium before the administration of viosterol. The spinal fluid or diffusible calcium represented 47 per cent of the total serum calcium after the administration of viosterol. The average diffusibility ratio prior to the administration of viosterol equaled

* 10,000 International Units per gram.

† 10,000 times average cod-liver oil, 1,000,000 International Units per gram; kindly supplied by Mead Johnson & Co.

127 per cent. After viosterol, 10,000 X, 0.5 cc. (20 gtts.) q. d., over a period from 8 to 15 days, the diffusibility ratio dropped to 96 per cent.

Comment.—It is obvious that viosterol increases most markedly the non-diffusible calcium and to a lesser extent the diffusible calcium. This is confirmed by a decrease in the diffusibility ratio which accompanies the administration of viosterol in cases of pulmonary tuberculosis.

It is evident that the untreated patient acutely ill with pulmonary tuberculosis has an increased diffusibility ratio, providing his intake and absorption of calcium and phosphorus is adequate. Likewise the patient, whose tuberculosis presents considerable healing and fibrosis, has a tendency toward a lower diffusibility ratio. Cantarow[23] states that the diffusibility ratio associated with a fibrotic lesion of low-grade activity is a subnormal one. We are inclined to assume that it is not subnormal, but rather one which approaches the diffusibility ratio of an individual with a normal calcium metabolism.

In previous work,[37] we observed that a more rapid clearing and fibrosis was evident in some cases of pulmonary tuberculosis after viosterol had been administered. An increase in non-diffusible calcium is present in patients with fibrotic lesions. Therefore these observations lead us to conclude that an increase in non-diffusible calcium favors the healing of pulmonary tuberculosis.

Summary. 1. Viosterol increases the calcium in the blood and spinal fluid of patients with pulmonary tuberculosis.

2. Viosterol increases both the diffusible and non-diffusible fractions of calcium. The non-diffusible fraction is the more affected.

3. In patients with pulmonary tuberculosis, viosterol reduces the diffusibility ratio by increasing the non-diffusible calcium.

Grateful acknowledgement and thanks are due Miss Grace Heimann of Boehne Hospital Laboratory for her valuable assistance.

BIBLIOGRAPHY.

1. Clark, E. P., and Collip, J. B.: J. Biol. Chem., 1925, **63**, 461.
2. Kramer, B., and Tisdall, F. F.: Bull. Johns Hopkins Hosp., 1921, **32**, 44.
3. Benedict, S. R., and Theis, R. C.: J. Biol. Chem., 1924, **61**, 63.
4. Schmidt, C.: Charakter der epidemischen Cholera, Rehr'sche Verlagsbuchhandlung, Leipzig, 1850.
5. Yvon, P.: J. Pharm. Chim., 1877, **26**, 240.
6. Mestrezat, W.: Ibid., 1909, **29**, 572.
7. Halverson, J. O., and Bergeim, O.: J. Biol. Chem., 1917, **52**, 837.
8. Kummer, R., and Minkoff, G.: Compt. rend. hebd. d. séances et mém. de la Soc. de Biol. de Bordeaux, 1921, **85**, 864.
9. Mann, S. A.: Arch. Neurol. and Psychiat., London, 1922, **8**, abstrs. Nos. 14–17.
10. Weston, P. G., and Howard, M. Q.: Arch. Neurol. and Psychiat., 1922, **8**, 179.
11. Leicher, H.: Deutsch. Arch. klin. Med., 1923, **141**, 196.
12. Depisch, F., and Richter-Quittner, M.: Wien. Arch. f. inn. Med., 1923, **5**, 321.
13. Pincus, J. B., and Kramer, B.: J. Biol. Chem., 1923, **57**, 464.
14. Barrio, N. G.: J. Lab. and Clin. Med., 1923–1924, **4**, 54.
15. Critchley, M., and O'Flynn, E.: Brain, 1924, **47**, 337.
16. Neustaedter, M., Hala, W. W., and Tolstoouchow, A.: J. Am. Med. Assn., 1925, **85**, 5.

17. Cameron, A. T., and Moorhouse, V. H. K.: J. Biol. Chem., 1925, **63**, 687.
18. Nourse, J. D., Smith, D. N., and Hartman, J. I.: Am. J. Dis. Child., 1925, **30**, 210.
19. Hamilton, B.: J. Biol. Chem., 1925, **65**, 101.
20. Merritt, H. H., and Bauer, W.: Ibid., 1931, **90**, 215, 233.
21. Cooper, F. B.: Am. Rev. Tuberc., 1931, **24**, 347.
22. Booth, J. D., and Broga, A. S.: Ibid., 1932, **25**, 231.
23. Cantarow, A.: Calcium Metabolism and Calcium Therapy, Lea & Febiger, Philadelphia, 1933.
24. Cohen, H.: Quart. J. Med., 1923–1924, **17**, 289.
25. Crimm, P. D., Strayer, J. W., Watson, H., and Heimann, G.: Am. Rev. Tuberc., 1933, **28**, 202.
26. Vines, H. W. C.: J. Physiol., 1921, **55**, 86.
27. Rona, P., and Takahashi, D.: Biochem. Ztschr., 1911, **31**, 336.
28. von Meysenbug, L., Pappenheimer, A. M., Zucker, T. F. and Murray, M. F.: J. Biol. Chem., 1921, **47**, 529.
29. Cruikshank, W. W. H.: Biochem. J., 1923, **17**, 13.
30. Loeb, R. F.: J. Gen. Physiol., 1923-1924, **6**, 453.
31. Tischimber, H., and Tischimber, C.: Compt. rend. Soc. de biol., 1924, **91**, 592.
32. Cushny, A. R.: J. Physiol., 1919–1920, **53**, 391.
33. Moritz, A. R.: J. Biol. Chem., 1925, **64**, 81.
34. Updegraff, H., Greenberg, D. M., and Clark, G. W.: Ibid., 1926, **71**, 87.
35. Lui, S. H.: Chinese J. Physiol., 1927, **1**, 331.
36. Neuhausen, B. S., and Pincus, J. B.: J. Biol. Chem., 1923, **57**, 99.
37. Crimm, P. D.: Am. Rev. Tuberc., 1932, **26**, 2.

REVIEWS.

APPENDICITIS. ITS ÆTIOLOGY AND PATHOLOGY. By LUDWIG ASCHOFF, Freiburg i. Br. With a Short Contribution on the Lymphatic System of the Human Appendix by DR. H. SENG. Translated by G. C. PETHER, M.D., M.R.C.P. Pp. 153; 36 illustrations. London: Constable & Co., Ltd., 1932. Price, 16/–.

THIS develops the view that appendicitis starts from an epithelial lesion, the inflammation spreading both as a phlegmon on the mucosa and as a wedge toward the serosa, with rapid longitudinal spread in the muscularis and serosa. It opposes Ricker's theory (1924), that the trouble is due to a reflex irritation of the nerves of the appendiceal vessels. Special attention is given in Dr. Seng's section to the peculiar lymphatic arrangement as supporting the above theory. The evidence for a special bacterial flora (non-hemolytic streptococci and pneumococci) in the distal portion as chief exciting causes is given in detail. While of great interest and strongly suggestive, it hardly warrants the deduction that the group of the intestinal streptococcus "may be regarded as *the* cause of appendicitis." As the same organisms are found in normal appendices, a hypothetical increase in virulence is invoked, favored by a stagnation of the secretion of the distal portion. In view of recent increases in appendiceal morbidity and mortality, this thorough presentation, well translated, merits careful study by practitioners even more than by pathologists.

E. K.

THE BRAIN AND ITS MECHANISM. By SIR CHARLES SHERRINGTON, O.M., G.B.E., F.R.S., Waynflete Professor of Physiology in the University of Oxford. The Rede Lecture delivered before the University of Cambridge, December 5, 1933. Pp. 35. New York: The Macmillan Company, 1933. Price, 50 cents.

THIS Rede Lecture at the University of Cambridge develops the picture of the brain as a wide nerve net made up of nerve threads with two kinds of action at the nodal points, one which fires the action of the thread (motor impulse), the other which impedes the firing. The travelling signal (excitant here indistinguishable from inhibitant) has been shown by Adrian to be "a brief local depolarization of the electrically polarized surface layer of the nerve thread." Yet the author does not presume to explain the manifold activities of the mind and affirms that the problem will long offer the clinically somewhat cold comfort that to journey is better than to arrive.

E. K.

THOMAS YOUNG, F.R.S., PHILOSOPHER AND PHYSICIAN. By FRANK OLDHAM, M.A., B.Sc., A. Inst. P., formerly Scholar of St. John's College, Cambridge. Pp. 159; illustrated. New York: Longmans, Green & Co., 1933. Price, $2.40.

To the reader who has known in a vague way that Sir Thomas Young was one of the greatest scientists of 150 years ago this concise but detailed account of his career and achievements will be a welcome acquisition.

Born of Quaker parents in the West Country, he could read at the age of 2, and knew "The Deserted Village" by heart at 6. An accomplished classicist and linguist, he has mastered Linnaeus, Newton and Lavoisier as well as his Corneille and Racine at 17. Before his death from arteriosclerosis at 56, he had elucidated the mechanism of accommodation, discovered astigmatism, established his Modulus (numerical ratio of stress to strain in a stretched material), advanced the wave theories of light and sound by his study of interference phenomena, discovered the eriometer principle of optically measuring the size of small particles, through his study of capillarity and cohesion made the first estimate of the size of atoms, and anticipated Champollion in most of the interpretation of the famous Rosetta stone. Truly an intellectual giant who fully deserves the words on his tablet in Westminster Abbey: "A man alike eminent in almost every branch of human learning." E. K.

NATURE AND NURTURE. By LANCELOT HOGBEN, M.A., D.Sc., Professor of Social Biology, University of London. Pp. 143. New York: W. W. Norton & Co., Inc., 1933. Price, $2.75.

METHODS are presented for studying human genetics and evaluating the relative influences of heredity and environment. Emphasis is placed on genetics as a branch of medicine; therefore, the behavior of the genes which determine mental defects and susceptibility to diseases which are incurable so far is stressed. Already more than 30 such diseases are known. The scope of the book is indicated by the chapter headings. Chapter I treats of the medical applications of genetical principles; those which follow with the solutions of the problems involved. Thus Chapter II deals with the "application and limitations of the theory of random mating;" Chapter III with "consanguineous parentage and the theory of inbreeding;" Chapter IV with "the genetic analysis of familial diseases;" and Chapter V with "the interdependence of nature and nurture." An analysis of human linkage data is given in one of the appendices.

Statistical methods are given for analyzing data from slow breeding organisms with few offspring where the matings are not controlled by the investigator. The methods are applied with a clear recognition of the fact that the accuracy of the conclusions drawn cannot exceed that of the assumption and hypotheses on which they are based. Thus the author points out that the assumption of random mating is not valid in certain cases, since gentlemen are reputed to prefer blondes. Or again, "A young woman with a strong belief in the sprinkling of babies may be inclined to reject the advances of a young man with an equally strong conviction in favor of immersion of believers." Inbreeding in isolated communities and among royalty and the presence of obvious physical defects form evident exceptions. Nevertheless, the assumption of random selection appears to be applicable generally in regard to characteristics which are not readily recognizable such as taste-blindness or isoagglutinins in the blood. The author states: "First it is necessary to establish the principle of random mating. Then we shall examine when it can be used successfully. Finally we must examine when it breaks down. A scientific law is only correctly stated when it contains within itself a recognition of its own limitations." The treatment of the evidence derived from a study of identical twins is the least satisfactory part of the book and needs to be buttressed by a study of the results obtained in this country by Newman and his coworkers.

This book presents a well-considered approach to the subject and is worthy of the attention of physicians, medical students and students of human heredity. E. C.

THE ROSE RESEARCH ON LYMPHADENOMA. First Volume. By SIR THOMAS HORDER and others. Pp. 136; 98 illustrations, many in color. Baltimore: William Wood & Company, 1933. Price, $7.25.

THE riddle of the etiology of Hodgkin's disease, called lymphadenoma in England, has remained unsolved since Thomas Hodgkin first described it in 1832. This volume records the results of work carried on between 1920 and 1930 at St. Bartholomew's Hospital, under the Rose Foundation, and since then under the Medical Research Council. The text opens with a brief but lucid description of Hodgkin's disease in its typical and atypical forms. H. M. Gordon's section on etiology describes the negative studies on spirochetes, fungi and tubercle bacilli.

In marked contrast to these negative studies was the search for a virus. Sterile broth suspensions of glands removed at biopsy were made; subcutaneous injection into rabbits yielded only inflammatory nodules. But when a 1 to 10 suspension, which had been macerated in the icebox for some days, was injected intracerebrally into rabbits, a striking syndrome of ataxia and spastic paralysis of the hind legs appeared in 2 to 6 days followed by wasting of these limbs and, in some cases, death of the animal. As controls, glands from cases of sarcoma, carcinoma, lymphatic leukemia, adenitis and hyperplasia were subjected to the Gordon test. None of these produced the encephalitis-like syndrome in rabbits.

The pathogenic agent appeared to be a virus of the same class as that of vaccinia. Tests on its filterability have been so far inconclusive.

By special mordants and stains, small granules similar to the Paschen bodies, which many believe to be the case of vaccinia, were found; this is suggestive but not conclusive. The agent withstands heat, phenolation and dseiccation very well. It will not transmit in series. It appears to be limited to glands from cases of Hodgkin's disease, and its presence, as revealed by rabbit test, will be useful for purposes of diagnosis, especially in obscure cases where the histologic picture is inconclusive.

The description of the lesions produced in the brain of rabbits injected with this organism is not very extensive. The lesions that are produced consist of a round-cell infiltration into the meninges and, around some of the bloodvessels in the cortex, a perivascular exudate of lymphocytes.

The third section of the book concerns the division of yeasts by complement-fixation methods into a limited number of serologic types. They appear to have nothing to do with lymphadenoma.

In the next section—blood studies of experimental animals—the evidence indicates that nothing of value can be learned from the hemoglobin and red blood corpuscles, but that the behavior of the leukocytes may prove to be useful.

The last section of the book, by B. D. Pullinger, describes the histology and histiogenesis of the disease in which the author supports the theory that the reticulum is the responsible tissue element in the construction of Hodgkin's disease and that endothelial cells are of no consequence. He adduces some evidence that the term reticuloendothelium is incorrect and inappropriate.

This is a handsome volume, well printed and finely illustrated. It is not a book for the general practitioner but is indispensable to one who desires to know thoroughly the recent work on Hodgkin's disease or who contemplates making use of the Gordon test as a diagnostic measure. It is to be regretted that some of the writers have not employed the elegant and attractive English that makes writings from their country so welcome and that develops scientific literature that reads like fiction. It may well be that the highly technical character of this discussion makes it difficult to use choice language, but a dry subject is often made easy of reading and understanding by elegant style. H. F.

BENIGN TUMORS IN THE THIRD VENTRICLE OF THE BRAIN: DIAGNOSIS AND TREATMENT. By WALTER E. DANDY, M.D., Adjunct Professor of Surgery, The Johns Hopkins University. Pp. 171; 120 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $5.00.

THIS monograph consists of 21 case reports from the author's surgical records of benign tumors in the third ventricle, including colloid cysts. Each case is excellently illustrated with photographs, ventriculograms and diagrams, by means of which the reader accompanies the author step by step through diagnosis and operative procedure. The importance of the ventriculogram in diagnosis is stressed. The book concludes with a chapter on analysis of signs and symptoms produced by these tumors.

M. McC.

THE CANCER PROBLEM AND ITS SOLUTION. By HASTINGS GILFORD, F.R.C.S. Pp. 59. London: H. K. Lewis & Co., Ltd., 1934. Price, Cloth, 2s 6d; Paper, 1s 6d.

PROCEEDING from the axiom that the cancer cell is a dedifferentiated cell, the result of premature degeneration of animal (human) tissue, the author urges that the fight against cancer be concentrated on the "degenerating circumstances which anticipate or prolong the course of degeneration and favor the occurrence of precancers." Specifically he considers an easy but not sternly practical philanthropy and an efficient sanitation (which increase the survival and reproduction of the unfit) and a disregard of Darwin's evolutionary principles, especially of the need for use as a requisite of development, as the chief contributory errors. The logical sequence of wider application of the tenets of eugenics or wholesale sterilization of the supposedly unfit are not mentioned. Considered strictly from the above point of view the book is stimulating. To the reader, especially the cancer student, it is not recommended that the assemblage of facts or the deductions therefrom be too closely analyzed.

E. K.

WILHELM CONRAD RÖNTGEN AND THE EARLY HISTORY OF THE ROENTGEN RAYS. By OTTO GLASSER, Cleveland Clinic Foundation. With a Chapter "Personal Reminiscences of W. C. Röntgen" by MARGRET BOVERI, Berlin. Pp. 494; 96 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $6.00.

IN 1931, the author brought out through Springer the German edition of the work which he has now translated, revised and enlarged in response to numerous requests. With material collected principally from the literature of 1896, the author plunges *in medias res* with an account of the great discovery. Unlike many that have had to wait years for recognition, it was heralded and confirmed throughout the civilized world even before its discoverer had spoken publicly about it (January 23, 1896, to the Physical Medical Society of the University of Würzburg). It is only in the 5th chapter that we come to the scientist and the man, to be followed by an especially sympathetic chapter of personal reminiscences by Margret Boveri. His modesty and reticence (he gave no lecture on receiving the first Nobel physics prize) are apparent throughout and the war gloom, with his death in 1923 during the inflation, carries its lesson. Chapters on the Roentgen rays in physics, in warfare, medical diagnosis and therapy and in non-medical directions add to the reader's interest in this extremely valuable record. In Chapter 23, the bibliography gives the astonishing number of 1044 books and pamphlets published on the subject in 1896 alone.

E. K.

THE THERAPEUTIC AGENTS OF THE QUINOLINE GROUP. By W. F. VON OETTINGEN, M.D., PH.D. Assistant Professor of Pharmacology, School of Medicine, Western Reserve University. Pp. 301. New York: The Chemical Catalog Co., Inc., 1933. Price, $6.00.

IN this American Chemical Society Monograph, the material is intended primarily for chemists and pharmacologists, but the presentation, involving structural formulæ and common as well as technical names, is such that the average physician will have no difficulty in following it. Emphasis is placed upon pharmacological actions and chemical details are omitted. Since some of these drugs are in everyday use (notably quinin, quinidin, and cinchophen), others represent high hopes that were not substantiated by wider experience (such as plasmochin and yatren), and others may be a starting point for new groups of local anesthetics (as nupercain), and antiseptics (the acridin dyes), physicians and surgeons will find much to interest them in this admirable monograph. C. S.

BIRTH CONTROL IN PRACTICE. Prepared Under the Supervision of a Scientific Advisory Committee. Text and Tables by MARIE E. KOPP, PH.D. With a Foreword by ADOLF MEYER, M.D. Pp. 290; 50 tables. New York: Robert M. McBride & Co., 1934. Price, $3.75.

THIS book, although obviously written for propaganda purposes, has the merit of confining itself strictly to the facts it presents. The text is rigidly factual, no opinions are expressed by the author, and it is a most accurate statistical report based on 10,000 cases of various aspects of the work in a large birth control clinic. Of special interest to those concerned in the Birth Control movement, it gives a precise account as to just what can and cannot be accomplished with modern contraceptive methods in a "Maternal Health Center."

The text is divided into six parts. The first is historical and descriptive. The second section deals with the pertinent aspects of the patient's social and economic history. Part three concerns itself with an analysis of the patient's various physical factors such as sex history, obstetric history, studied by the statistical method, much of which in my opinion might well be omitted. The frequency of abortions (69% induced) is evidenced by the statement that "more than 1 in 4 pregnancies was terminated spontaneously or was intentionally interrupted." In part four, the one weak feature is an unconvincing summary of the medical indications for prescribing contraceptives. The technique of the various contraceptive methods prescribed at the clinic is well given together with an illuminating compilation of the results that have been secured. Here lies the real justification for the book, as it sticks rigidly to facts, and such questions as how often will the ignorant and illiterate use contraceptive methods, how effective is one method compared to another, etc., can be answered with accuracy from a series of cases large enough to eliminate the personal equation.

The book closes with a good summary and a series of statistical tables.
O. T.

LIFE OF CHRISTIAN SAMUEL HAHNEMANN. Founder of Homœopathy. By ROSA WAUGH HOBHOUSE, with a Preface by SIR JOHN WEIR, K.C.V.O., M.B. Pp. 288; illustrated. London: The C. W. Daniel Company, 1933. Price, 7/6.

HAHNEMANN was undoubtedly sincere in his effort to learn "if God had not indeed given some certain law by which the diseases of mankind could be cured." Undoubtedly, also, the harmless methods of treatment

that he advocated were of great importance in combating the harmful polypharmacy that had so long existed. Thus his name will live in medicine's story, and whether or not the reader agrees with the principles of homeopathy, he will surely be interested in this clear portrayal of a consecrated life. Many too will doubtless be surprised to read that Hahnemann regarded removal or destruction of the fundamental cause of the disease "as the most elevated way that practical medicine could follow if it had sufficient knowledge." ("Curative Power of Drugs.") Also he recognizes that if fundamental knowledge of the cause of an acute disease and how to remove it be lacking, the symptoms may properly be combated by "temporary remedies . . . . which produced an opposite condition." ("Organon.") The arguments for *similia similibus* and the increasing potency of increasing dilutions ("potentisation"), it must be confessed, seem painfully weak; neither does the attempt to use the Arndt-Schulz law as a support seem justified. As a demonstration of the truth of homeopathic philosophy, this book does not carry conviction; as a portrayal of an extraordinary personality and an important development in 19th century medicine, it is well worth while. E. K.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 365; 54 illustrations, including 2 plates. Philadelphia: P. Blakiston's Son & Co., 1934. Price, $3.50.

THE rapid changes and advances in this complex subject make a "Recent Advance" volume particularly useful, especially as endocrinology is a topic which seems to lend itself easily to romance. The author has achieved his difficult task well. Anatomy, physiology, pathology, medicine and surgery have all contributed their quota to knowledge here detailed of the various endocrine organs in health and disease. To this the 801 references testify—a good half of these apparently being from the present decade. The final chapter on Interrelations is especially to be commended for its sanity and conservatism. E. K.

AMERICAN UNIVERSITIES AND COLLEGES. Edited by JOHN HENRY MACCRACKEN, for the American Council on Education, Washington, D. C. Pp. 1066. Second edition, revised and enlarged. Baltimore: The Williams & Wilkins Company, 1932. Price, $4.00.

THIS *multum in parvo* presents not only a general exposition of American higher education (284 pages) but also details of organization, requirements, resources, size of faculties, attendance, degrees conferred, etc., of the 521 accredited institutions (690 pages). The 17 appendices are concerned with the American Council on Education (by whom the book was prepared), 9 other educational associations, the Library of Congress, foreign students and available scholarships, and, last but not least, more than 2 pages of the various university degrees mentioned in the volume. Since the 1st edition (1928), 126 institutions have been added and the data of the rest submitted to their own officials for correction. Nevertheless, or perhaps on this account, there is a distinct lack of uniformity in presenting the pictures, especially of the larger institutions, tending to difficulties of comparison at least for the casual reader. One can safely say, however, that the book accomplishes its purpose of supplying an accurate and comprehensive picture of American higher education. E. K.

BOOKS RECEIVED.

NEW BOOKS.

Appendicitis. Its Ætiology and Pathology. By LUDWIG ASCHOFF, Freiburg i. Br. With a Short Contribution on the Lymphatic System of the Human Appendix by DR. H. SENG. Translated by G. C. PETHER, M.D., M.R.C.P. Pp. 153; 36 illustrations. London: Constable & Co., Ltd., 1932. Price, 16/–. (Review, p. 563.)

The Renaissance of Medicine in Italy. By ARTURO CASTIGLIONI, M.D., Professor of the History of Medicine at the University of Padua. The Hideyo Noguchi Lectures. Publications of the Institute of the History of Medicine, The Johns Hopkins University, Third Series, Volume 1. Pp. 91; 1 illustration. Baltimore: The Johns Hopkins Press, 1934. Price, $1.50.

Alcohol. Its Effect on Man. By HAVEN EMERSON, M.D., Professor of Public Health Practice, Columbia University. Pp. 114. New York: D. Appleton-Century Company, 1934. Price, $1.00.

The Cancer Problem and Its Solution. By HASTINGS GILFORD, F.R.C.S. Pp. 59. London: H. K. Lewis & Co., Ltd., 1934. Price, cloth, 2s 6d; paper, 1s 6d. (Review, p. 566.)

Mystery Magic and Medicine. By HOWARD W. HAGGARD, M.D., Associate Professor of Applied Physiology, Yale University. Pp. 192; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., 1933. Price, $1.00.

Jubilee Edition, Deutsche medizinische Wochenschrift, January 5, 1934. Pp. 88; illustrated, some colored. Leipzig: Georg Thieme, 1934.

Articles by v. Krehl, Kolle, Aschoff, Umber, Heine, Morawitz and others only less well known make this, indeed, a noteworthy jubilee number. A beautiful colored plate of inflammations of the iris demands attention even under the concealing title of Regenbogenhaut.

The Anatomy of the Rhesus Monkey (Macaca mulatta). By various contributors. Illustrated by BENJAMIN KOPEL. Edited by CARL G. HARTMAN, Department of Embryology, Carnegie Institution of Washington, and WILLIAM L. STRAUS, JR., Department of Anatomy, The Johns Hopkins University, Baltimore. Pp. 383; 125 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $6.00.

Human Sex Anatomy. By ROBERT LATOU DICKINSON, M.D., F.A.C.S. Pp. 145; more than 1000 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $10.00.

The Medical Clinics of North America, Volume 17, No. 1 (Cleveland Clinic Number—January, 1934). Pp. 253; 53 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, Clinic Year: paper, $12; cloth, $16.

The Brain and Its Mechanism. By SIR CHARLES SHERRINGTON, O.M., G.B.E., F.R.S., Waynflete Professor of Physiology in the University of Oxford. The Rede Lecture delivered before the University of Cambridge, December 5, 1933. Pp. 35. New York: The Macmillan Company, 1933. Price, 50 cents. (Review, p. 563.)

Thomas Young, F.R.S., Philosopher and Physician. By FRANK OLDHAM, M.A., B.Sc., A. Inst. P., formerly Scholar of St. John's College, Cambridge. Pp. 159; illustrated. New York: Longmans, Green & Co., 1933. Price, $2.40. (Review, p. 563.)

Annals of the Pickett-Thomson Research Laboratory, Vol. 9, Monograph XVI, Part I. Influenza. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 640; 28 plates of illustrations, various charts and tables. Baltimore: The Williams & Wilkins Company, 1933. Price, $12.50.

Krebs im Lichte biologischer und vergleichend-anatomischer Forschung. 1. Band. Ectodermkrebs. Pp. 192; 43 illustrations. Leipzig: Franz Deuticke, 1934. Price, M. 10.

NEW EDITIONS.

A Diabetic Manual. By ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Medical Director, George F. Baker Clinic for Chronic Disease at the New England Deaconess Hospital, etc. Pp. 224; 49 illustrations. Fifth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $2.00.

This very practical and entertainingly written book is invaluable to the diabetic patient in explaining to him clearly and scientifically the nature of his disease and the way in which his intelligent cooperation is vital in his treatment. Illustrations make vivid the explanations. This manual is of great value to the physician as well, in directing him in the ways of instructing his patients.

Human Embryology and Morphology. By SIR ARTHUR KEITH, M.D., F.R.S., LL.D., D.Sc., F.R.C.S. (ENG.), Master of the Buckston Brown Research Farm, etc. Pp. 558; 535 illustrations. Fifth edition. Baltimore: William Wood & Company, 1933. Price, $10.00.

Recent advances, particularly in the interpretations put on the significance of observed facts, have required a thorough revision since the appearance of the last edition in 1923. A new chapter has been added on Spemann's localized embryonic areas known as "Organizers" and the chemical substances by which they exercise their influence. The relatively small print and concise style together with the eminence of the author combine to make this book a splendid source of reference.

Fundamentals of Biochemistry. By T. R. PARSONS, B.SC. (LOND.), M.A. (CANTAB.), Sidney Sussex College, Cambridge. Pp. 435; 26 illustrations. Fourth edition. Baltimore: William Wood & Company, 1933. Price, $3.00.

The fact that a fourth edition has appeared within a little over a decade speaks for the continued popularity of Parsons' work. This very useful little book is warmly to be recommended to those who would like a brief and modern account of the principles of biochemistry.

Neuroanatomy. By J. H. GLOBUS, B.S., M.D., Associate Professor of Neuropathology and Neuroanatomy, New York University and Bellevue Hospital Medical School, etc. Pp. 229; 37 text illustrations and 53 plates. Sixth edition, revised and enlarged. Baltimore: William Wood & Company, 1934. Price, $3.50.

The author in the preface to the first edition makes this statement: "The structure of the central nervous system is considered by many a student and teacher as the most intricate and difficult branch of human anatomy. This unjustified belief is very likely the result of the old methods of approaching the subject of neuroanatomy." The appearance of a sixth edition of Globus' book indicates that he has succeeded in providing a guide which many have found useful.

American Universities and Colleges. Edited by JOHN HENRY MACCRACKEN, for the American Council on Education, Washington, D. C. Pp. 1066. Second edition, revised and enlarged. Baltimore: The Williams & Wilkins Company, 1932. Price, $4.00. (Review, p. 568.)

Laboratory Medicine. By DANIEL NICHOLSON, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba, etc. Pp. 566; 124 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $6.50.

Hypertension and Nephritis. By ARTHUR M. FISHBERG, Associate Professor to Beth Israel Hospital; Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 668; 39 illustrations and 1 colored plate. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $6.50.

Traitement des Maladies Rhumatismales par la Sanocrysine. By KNUD SECHER, Médecin-Chef à l'Hôpital de Bispebjerg, Copenhague. Pp. 84; 25 illustrations. Second edition. Copenhagen: Levin & Munksgaard, 1933. (Price not given.)

A System of Clinical Medicine. By THOMAS DIXON SAVILL, M.D., London. Edited by AGNES SAVILL, M.D., assisted by E. C. WARNER, M.D. Pp. 1063; 162 illustrations. Ninth edition. Baltimore: William Wood & Company, 1933. Price, $9.00.

Pfitzner's Leitfaden für Situsübungen an der Leiche. By DR. MED. K. O. HENCKEL, Professor an der Universität Concepción (Chile). Pp. 36. Eighth edition. Leipzig: Franz Deuticke, 1934. Price, M. 1.20.

A compendium of the anatomy of the chest and abdomen; not suitable for use in this country.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
CHARLES C. NORRIS, M.D.,
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,
AND
FRANK B. BLOCK, M.D.,
SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

TREATMENT OF CANCER OF THE CERVIX.

BY FRANK B. BLOCK.

IN this brief review of the extensive recent literature on uterine cancer it is obvious that of contemporaneous opinion only a general summary may be presented; but an effort will be made to show the possibilities of treatment, supplemented when desirable by statistical confirmation. The importance of this subject appears in HIRST's (*J. Am. Med. Assn.*, 1933, **101**, 897) address, in which he points out that 1 of every 8 women who reach the age of 35 will have a cancer and that the disease ranks second among the causes of death in America. The mortality is increasing, rising from 63 to 96 per 100,000 in 7 years (more than 50%). Of cancers in women, over 25% are in the genital organs, 80% of which are in the cervix uteri. Furthermore, of 4 women who come to a physician with cancer of the cervix, 1 may survive. Class I of the League of Nations classification of cancers of the cervix in which the disease is confined to that locality has a 50 to 80% 5-year recovery rate; Class IV, in which vagina, bladder and bowel are also involved, a rate of 2% or less. The whole problem of securing better results resolves itself at present, therefore, states Hirst, into the best means of recognizing the disease early. He calls attention to Schiller's test with the use of Hinselmann's colposcope as an important aid to an early diagnosis. The colposcope may be replaced by the more economical and portable binoculars with spectacle attachment. In the treatment of cervical cancer the high mortality of the radical operation, the negligible mortality of radium application, the approximate equality of results, the shorter hospitalization, the absence of suffering, the palliation of symptoms, and the fact that radium alone can be considered in advanced cases have relegated surgery to a subordinate place, although it cannot be ignored. The operation is as difficult as any in surgery and has a mortality of 16 per

cent in the hands of expert surgeons. Wertheim himself in the first 1000 of his 1500 operations had a mortality of 16%, as did Bonney in his first 227. Although both reduced their mortality to 9%, few could hope to rival them. The advantage of the radical operation lies in the removal of the regional pelvic glands, 21% of which were cancerous in Wertheim's statistics, 43% in Bonney's and 50% in Heyman's. The advocates of radium treatment are in the great majority. Almost all the prominent gynecologic clinics of the world have deliberately turned from surgery in cancer of the cervix to radium. A hopeful sign is that the operability of cervical cancers is increasing and the rate of cure has risen from 17% to over 28% in the past 5-year period.

Radiotherapy.—In Fukuoka, Japan, the IKEDAS (*Zentralbl. f. Gynäk.*, 1933, **57**, 1651) have treated with radium 620 cases of carcinoma of the cervix between the years 1914 and 1927. These cases represent slightly less than one-half of the cases seen, the others being too far advanced to permit of radiotherapy. There were 238 cases in the operable group with 5-year cures in 151 (63.45%). In Group 2 (borderline cases), there were 79 cases with 5-year cures in 60 (75.95%). In Group 3 (inoperable cases), there were cures in 41 of 248 cases (16.53%), while in Group 4 (incurable cases), in spite of their apparently utterly hopeless condition, cures were obtained in 3 of 55 cases (5.45%). Taking the entire group of 620 cases, healing for from 5 to 18 years (personally observed) was obtained in 255 cases (41.13%). Of the cases which had recurrences, the most frequent sites were the local and parametrial tissues and then the inguinal, iliac and mesenteric glands. In 4 cases, recurrences occurred in glands of the neck. In 8 cases, the carcinoma was complicated by myomata, and in 2 by ovarian cysts. Radiotherapy had a good influence on the myomata, stopping bleeding and causing atrophy of the tumor, but had no effect on the ovarian cysts. There were 13 cases in which the carcinoma was associated with pregnancy. Of 6 cases which were in the second half of pregnancy, 5 gave birth to children which have developed normally for from 5 to 18 years, while in 1 case there was a stillbirth. When the associated pregnancy is in the first half of gestation, there is a greater tendency to abortion following irradiation, since of the 7 cases in this series, all terminated their pregnancies after radium treatment.

In considering the value of a mode of treatment, WARD (*Surg., Gynec. and Obst.*, 1933, **57**, 546) emphasizes the essential differences between cancer of the cervix and cancer of the uterine fundus. In about 10% of cases, cancer originates in the cavity of the uterus, usually as adenocarcinoma. Cancer of the fundus is more frequent after the menopause, the mean age incidence being 8 years more than in cancer of the cervix. The ordinary panhysterectomy gives an average cure rate of 60% in these cases, and is, therefore, the method of choice; but unfortunately on account of obesity, senility, cardiovascular disease and diabetes, many of these patients are poor surgical risks, so that we must resort to intrauterine radium therapy and Roentgen ray, which give a cure rate closely approaching surgery. He believes that in these patients the ideal method is to combine radiotherapy and surgery when possible. In carcinoma of the cervix, all authorities agree that surgery is of little avail unless the radical operation of the Wertheim

or Schauta type is employed, which can be done only in operable cases. For the inoperable class, which includes more than 50% of those seeking relief, surgery has nothing to offer. Ward believes that in competent hands radium therapy combined with high-voltage Roentgen ray therapy gives results in advanced cases which are fully equal to the results obtained by surgery in operable cases, the primary mortality rate being less than 2% as compared to the 8 to 17% mortality of radical surgery. For the inoperable cases, radium therapy gives an average 5-year cure rate of 12 to 18% and has in the majority of cases a definite value in the palliation and prolongation of life. A 5-year cure rate of approximately 25% may be obtained in carcinoma of the cervix by either radical surgery or radium therapy in all those applying for relief. In the early cases, in which the disease is limited to the cervix, a 50% 5-year cure rate may be expected. The radical Wertheim operation requires skill and experience to be properly performed, and it must not be confused with the usual operation of complete or panhysterectomy which is frequently done for cancer of the cervix. The difference between an ordinary hysterectomy and the radical operation may be readily understood when compared to a simple mastectomy or the modern radical operation for cancer of the breast. He states that simple hysterectomy for carcinoma of the cervix is followed by fatal recurrence in nearly 100% of the cases. The safe use of radium, however, requires judgment and experience. A thorough understanding of its action and an appreciation of the complexities of its safe and efficient application is necessary. If a correct dosage and filtration is used, the cancer cells will be destroyed, but *not* the normal tissues. If too great a dosage and insufficient filtration is employed, the normal structures will also be destroyed, producing extensive necrosis, septic absorption, hemorrhages, fistulas and perhaps death. If too small a dosage is used, there will be a failure to destroy all the cancer cells. The foregoing statements of Ward, coming from one who is well qualified to handle these cases either from the surgical or the radiotherapeutic angle, are of special interest as they reflect the present thoughts on this subject in the Woman's Hospital in New York, where the results of treatment of cancer of the cervix are probably as good as in any institution in this country, or in the world.

Prognostic Value of Histologic Grading.—Much has been written in the past decade concerning the prognostic value of the histologic pictures of the growth to be treated. From recent reports the enthusiasm which greeted such opinions when they were originally presented is not warranted. MALIPHANT (*J. Obst. and Gynec. Brit. Emp.*, 1933, **40**, 444) studied the relation between cellular structure and response to radium treatment in a series of 236 cases of cancer of the uterine cervix, the growths being divided histologically into solid and glandular forms, with a subdivision of the former into three groups according to the predominant type of cancer cell. Of these growths, 4.2% were adenocarcinomas, and of the remainder 30.9% were spinal-cell cancers, 55.8% were transitional-cell cancers and 13.3% were spindle-cell cancers. Only 21% of the growths presented pure cell forms; in the remainder the grouping was based on the predominant type of cell present. The best immediate response to treatment was seen in the

spindle-cell cancers. The radiosensitiveness of the different histologic forms of cancer of the cervix is still unsettled, but the results of this investigation support to some extent the biologic relation between anaplasia and radiosensitivity. Though the spindle-cell cancers showed the best immediate results, the cellular type of the growth seemed to make but little difference so far as results were concerned. This may be accounted for by the balancing of the two factors of the malignant condition and radiosensitivity in the 4 histologic groups. Though the results in the 4 groups are practically equal, there are small differences which are noteworthy, since the results obtained in the group of adenocarcinomas were a little better than they were in the epidermoid cancers. The results in the solid carcinomas improved slightly with the degree of anaplasia of the tumor. He concludes from his study that, though the cytologic examination of the tumor would have supplied some information with regard to its immediate response to radium irradiation, it would not have been of any assistance in arriving at an ultimate prognosis.

A similar opinion has been expressed by JORSTAD and AUER (*Surg., Gynec. and Obst.*, 1933, **57**, 583), working in the Barnard Free Skin and Cancer Hospital, St. Louis. From an analysis of the grading of all the cancers of the cervix treated by radium from 1917 to 1927 in the above hospital, they conclude that grading alone is of no prognostic value. However, they state that grading may be of great value in the radium treatment of these tumors, since the cases in Grades 1 and 2, which show more differentiation of cells, are much more radioresistant than the cases in Grades 3 and 4, which show more immature cells, so that, while the latter grades are more malignant, they are more responsive to radium irradiation. Grading may be the deciding factor in the decision to employ surgical treatment rather than radium therapy.

Injuries to Urinary Organs by Irradiation.—That radium irradiation has definite potentialities for harm which are not always appreciated by the inexperienced is shown by Dean's (*J. Urol.*, 1933, **29**, 559) report calling attention to the delayed radium burn of the urinary bladder. In his series of 47 cases, this caused symptoms in from 10 to 114 months after the radium treatment had been given. The lesion is really the result of an obliterative endarteritis and consists of a white avascular central area surrounded by a zone of dilated bloodvessels. In some cases the center breaks down and forms an ulcer. The onset of symptoms, though characteristically long delayed, is usually sudden and consists of frequency, dysuria and hematuria with severe pain. At times the hemorrhage is severe enough to threaten life. The diagnosis is easy if the possibility of the condition is kept in mind and is based on the history of previous irradiation and the local findings by cystoscopy. Biopsy may be necessary as the picture may closely simulate carcinoma. The ulcers which are present in two-thirds of the cases are located in the posterior third of the base of the bladder, almost in the midline. Before ulceration occurs the prognosis is good, but when ulceration is extensive the prognosis must be guarded. The prophylaxis of the lesion is the use of the minimal amount of irradiation necessary for cure and proper shielding of the bladder. The treatment of the developed lesion is the relief of pain and treatment of the infection.

Pain may usually be relieved by teaspoonful doses of tincture of hyoscyamus, every 4 hours, and occasionally the use of codein. Heat and rest are important and lavage of the bladder with 1 or 2% of phosphoric acid is of use. The phosphoric acid may be increased gradually to a 5% strength as the bladder becomes more tolerant and treatments are given at increasing intervals until healing is complete, which may take many months. Another type of radium injury, though not so common, reported by COUNSELLER (*Proc. Staff Meet. Mayo Clinic*, 1933, **8**, 533) is the formation of an enterovaginal fistula following the application of radium to the cervical stump. In this case, 7 years after subtotal hysterectomy for fibroids, a yellowish-brown discharge from the vagina was noted. A year later, with the diagnosis of carcinoma of the cervical stump, radium was applied for 12 hours. Within 3 months a vaginal intestinal fistula had developed which did not close during the following 2 years. Operation was then undertaken, and when the abdomen was opened it was found that the ileum was attached to the vagina about 60 cm. from the ileocecal valve, and at this point there was a fistula into the vagina just under the cervical stump. There were no other adhesions or evidences of remaining malignancy in the pelvis, and separation of the bowel and closure of the fistula was successfully accomplished. He believes that the fistula in this case was undoubtedly due to the fact that a loop of small bowel became adherent to the vagina following hysterectomy 7 years prior to the development of the carcinoma in the stump rather than because radium had been misapplied. About 100 cases of cancer of the cervical stump have been observed at the Mayo Clinic, and it is the custom to treat these lesions with radium.

Results of Surgical Treatment.—In the report of SCHILLING (*Zentralbl. f. Gynäk.*, 1933, **57**, 2422) from the gynecologic department of the University of Leipsic, under the direction of Stoeckel, there were 465 cancers of the cervix treated between 1923 and 1926. The Wertheim operation was performed on 35, of whom 11 (31%) were free from recurrence after 5 years and the primary mortality was 20%. Most patients were irradiated with radium before operation, and all had had postoperative Roentgen ray treatment. In 150 cases the radical vaginal hysterectomy of Schauta (Stoeckel modification) was done, of whom 87 were free from disease 5 years later (58%) and the primary mortality was 4%. In 287 patients, irradiation alone was employed, of whom 59 (20%) were free from disease for 5 years or longer and the primary mortality was 1.4%, being due to embolism, sepsis, peritonitis or heart disease. The dosage of radium was between 2000 and 4000 mg. hours, given in a short time and usually supplemented later by deep Roentgen ray therapy of from 95 to 110% erythema dose. Classifying the cases by the degree of involvement, irrespective of the method of treatment employed, it is shown that Group 1 contained 126 cases, with 46% cures; Group 2, 119 cases, with 43% cures; Group 3, 154 cases, with 18% cures; and Group 4, 60 cases, with 15% cures. In 8 cases the cancer was complicated by pregnancy, and of these 3 remained free from recurrence over 5 years. From the above statistics it may be readily seen that the best results in this clinic have been obtained by the use of the radical vaginal hysterectomy, with a

mortality rate so low as to fully justify the continuation of such treatment in the trained hands which make up the personnel of that organization. There are, however, not many clinics which can approach a 5-year cure rate of 58% from this operation.

Operation Combined With Irradiation.—In order to get the maximum effect from irradiation, two methods have been presented in which the operation is performed and irradiation is directly applied to the carcinomatous growth. In the first method, described by CURTIS (*Am. J. Obst. and Gynec.*, 1933, **26**, 569), the necrotic cervical growth is treated with surgical diathermy or prophylactic radiation at least 3 weeks prior to operation. Preliminary deep Roentgen ray therapy may serve equally well in healing the sloughing cancerous surface. When the surface has become free from necrosis and infection, a pelvic examination is made under anesthesia to determine the extent of the growth and the amount of intervention required, and surgical exposure of the cancer-bearing uterus and adjacent cellular tissues is undertaken. With blunt dissection the bladder is mobilized upward, the cervix being encircled with an incision as in making a radical vaginal hysterectomy, and the vaginal mucosa is painstakingly dissected laterally and posteriorly, along natural lines of cleavage. The body of the uterus and the regions of the broad ligaments and cardinal ligaments are now well visualized. With the organ half delivered broadside, vaginally, the bladder safely anchored in its elevated position with a catgut suture holding it high on the uterus, and the paracervical tissue exposed, a massive radium treatment is possible. Radium needles or radon seeds are now inserted where needed, near to or into the cervix or far from it, as indicated, with assurance of safety of the adjacent vulnerable organs. Although the ureters are subject to possible injury, they are considerably retracted incident to the dissection and displacement of the bladder and are relatively immune. Preliminary ureteral catheterization may merit consideration in selected cases, but Curtis has not resorted to it. Injury of a uterine artery is a possibility, but he has not seen that complication despite many years' custom of introducing radium needles into the cervical parametrium. Palpation of the artery preliminary to burying a radium needle in its vicinity appears unnecessary. After burying the radium needles, as described, a chain tandem of radium capsules is inserted into the uterine canal in the usual manner and a vaginal pack completes the procedure. The above method of treatment is advocated for cases in Group 2 or to the less advanced cases in Group 3 in which there is some hope of cure.

In the second method of operation combined with direct irradiation, described by SCHUMANN (*Am. J. Obst. and Gynec.*, 1933, **26**, 260), advanced cases of pelvic carcinoma are attacked by applying Roentgen rays directly to the affected tissues without the intervention of the abdominal parietes. The procedure is carried out in connection with the implantation of radium in the cervix or the uterine cavity, as the case may require, and has only been applied in instances where the entire pelvis is a mass of carcinomatous tissue, with extension into the adjoining lymph nodes. The technique of this procedure consists in placing the patient in the lithotomy position for the performance of a

biopsy and the application of 50 mg. radium to the cervix or uterine cavity. The patient is then placed in the Trendelenburg position and a median abdominal incision is made about 6 to 8 inches in length, and the abdominal walls are widely retracted by means of a Balfour retractor. The intestines are carefully walled off with a large gauze pad, after which the abdominal wall and all the pelvic tissues except those involved in the malignant growth are protected from irradiation by being covered with sheet lead, 2 mm. in thickness. A roll of such sheet lead and a large heavy scissors are in readiness, having been sterilized by boiling. Strips of lead are cut to fit the interior of the abdomen and are then snugly molded into position (with the fingers) so as to isolate the tumor area absolutely, all other tissues being covered by strips of lead. A large sterile dressing is then applied, and the patient transported to the Roentgen ray room, where she is given a full therapeutic dose of Roentgen ray irradiation, *i. e.*, 150 ma., 18-inch distance, 130 kv., 6 mm. aluminum filtration. Upon the completion of the treatment the sterile dressing is replaced, the patient is wheeled back to the operating room, the lead and gauze packs are removed and the incision is closed. No attempt is made to remove any of the malignant tissues. The operation is much facilitated when a light and simple operating table is used and avertin is the anesthesia of choice, because the patient lies quietly asleep during the entire procedure and time is not a particular factor.

Pelvic Sympathectomy for Pain.—In cases of inoperable carcinoma of the cervix, where the patient suffers from constant pain, the operation of pelvic sympathectomy has been successfully employed in several clinics both in this country as well as abroad, where the procedure was first advocated. COTTE (*Zentralbl. f. Gynäk.*, 1933, **57**, 72, 77), of Lyon, has resected the presacral nerve in over 200 cases with results that appear to be very satisfactory, although in the majority of his cases the pain was due to other conditions than malignant disease. He has never had any bad results which could be attributed to the operation, such as bladder disturbances or secondary trophic changes in the vagina or vulva, though since his first operation was performed more than 7 years ago, ample time has elapsed for these changes to appear. The largest series that has been reported in this country is that of GREENHILL and SCHMITZ (*J. Am. Med. Assn.*, 1933, **101**, 26), who have performed the operation on 13 patients with inoperable carcinoma of the cervix. They removed portions of the presacral nerve (superior hypogastric plexus), varying in length from 5 to 10 cm., making certain that nerve tissue was present by microscopic examination. They regarded the results as most satisfactory because all of the 11 patients who survived the operation experienced relief from pain. Three women had temporary diarrhea for a few days after the operation and 3 women developed paresthesia in the back of the thigh and popliteal space, but no bladder disturbances were observed. Two patients died, both on the 25th day after operation, 1 from cachexia and the other from bronchopneumonia and cachexia, but both were entirely relieved of their pain. They comment upon the fact that the term "presacral nerve" is a misnomer and apt to be confusing since the structures to be removed are prelumbar rather than presacral and also

are arranged in the form of a plexus rather than as a single nerve. The term superior hypogastric plexus is more accurate. The technique of this operation is not complicated and well within the field of the gynecologic surgeon, as opposed to the operation of cordotomy, which has more dangerous possibilities and belongs entirely within the field of the neurosurgeon. This operation has been performed by BEHNEY (*Am. J. Obst. and Gynec.*, 1933, **25**, 687) on 7 patients who were in extreme pain from Stage 4 carcinoma of the cervix. Complete and permanent relief of pain in the lower abdomen and thighs was secured in 5 patients, while in 2 cases the operation failed to give relief. All incisions healed by first intention and there were no postoperative complications. In spite of the extensive involvement of the bowel with metastatic carcinoma, the slight amount of distention and gas pains was a striking feature. In fairness to the operation, Behney states that in 1 of the cases which failed to get relief, the omentum was so densely adherent to the iliac vessels that exposure of the sympathetic plexuses was impossible, while in the other unrelieved case he feels that he failed to include all of the afferent fibers in the tissue which he removed. In other words, relief cannot be expected from a nerve resection of this type unless all of the afferent fibers are interrupted. Another enthusiastic report of this operation has been presented by WETHERELL (*J. Am. Med. Assn.*, 1933, **101**, 1295), who presents his experiences in 7 cases, only 2 of which were cases of pain due to inoperable cervical cancer. He believes that the operation is entirely safe and well worth while when pain can no longer be relieved by medication. (Sympathectomy is not uniformly successful, but, as Behney has stressed, it is a valuable operation in certain carefully selected cases. C. C. N.)

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA.

MYCOTIC INFECTIONS OF THE SKIN.

A RÉSUMÉ OF CURRENT CONCEPTION.

By JOHN H. STOKES.

THE range of literature covered in this summary includes certain of the basic contributions as far back as 1929, but the larger part of the material is drawn from the years 1931 to 1933.

Mycotic infections comprise approximately 10% of the general clientele of dermatologic clinics. GOODMAN (*Arch. Dermat. and Syph.*, 1931, **23**, 872) pointed out the inverse relation between eczema and mycotic infections, which is characteristic of the diagnostic trend of

the times; eczema decreasing in frequency from 25% in 1925 to 11% in 1929, while mycotic infection increased from 3% in 1925 to 10% in 1929. For European clinics the experience of SCHMIDT (*Arch. f. Dermat. u. Syph.*, 1933, **169**, 259) is fairly typical. Mycotic infections constitute 10% of the patient material, and 50% of these mycotic infections involve the hands and feet. There has been a gradual increase in the incidence of this group of diseases in the last several years. Groups of students studied in widely separated parts of this country are represented by the reports of LEGGE, BONAR and TEMPLETON (*Arch. Dermat. and Syph.*, 1933, **27**, 12) and MUSKATBLIT (*New York State Med. J.*, 1933, **33**, 632). These authors give figures ranging from 50 to 89% of men showing clinical evidence of infection and 15 to 17% of women. The first-named authors attribute the sex variation to difference in gymnasium conditions and point out the increase from 51 to 78% in the men during a semester of gymnasium work. Weidman, in discussion, however, stated that the opposite conditions obtained in his studies and attributed the difference to sex and susceptibility. In CREMER'S report (*Arch. f. Dermat. u. Syph.*, 1933, **169**, 244) on Amsterdam conditions found 84% of students had clinically suspicious lesions.

The reported incidence varies greatly with the criteria employed for diagnosis. The presence clinically of fissuring and eczematoid eruptions between the toes is the source of the high figures mentioned. When culture is employed, however, as the most authentic diagnostic criterion, the proportion of positives varies widely, depending presumably upon expertness in laboratory facilities, from 14% in Cremer's series, just mentioned, and 17.9 per cent in that of Muskatblit, to the higher proportions of positive cultures obtained in those cases in which it was possible microscopically to demonstrate the fungus in scales, as, for example, Muskatblit's 50.8% and a variety of figures cited by Schmidt ranging from 30 to 85%. The striking difference between the cultural results on hands and feet is illustrated by Schmidt's 23.4% positive cultures on the hands, as against 73% positive cultures on the feet. The difference is attributable to the absence of fungi in the so-called dermatophytid of the hands, as will presently be explained.

Pathogenesis—Dermatophytoses and Dermatophytids.—The conception of the "id" extended from the field of cutaneous tuberculosis by Jadassohn and Guth is one of the most important recent aspects of dermatomycology. In accordance with this conception, no inconsiderable part of the visible eruption of a dermatophytosis is a secondary sensitization phenomenon or dermatophytid in which no fungi are present—a dermatitis attributable to toxic or allergic reaction, from a primary focus sometimes distinguished with difficulty clinically from the general eczematous picture presented by the patient. A large proportion of the primary foci, or dermatophytoses proper, in which the fungi are present, are situated upon the feet, in the flexures of the groin, the anogenital cleft, and similar situations suitable for the growth of the fungus, while the secondary sensitization eczema and other "id" manifestations may be found upon the ears, the face, the palmar and dorsal surfaces of the hands and in the form of more or less widely distributed dermatitic eruptions on the trunk and lower extremities. In addition to the eczematoid dermatophytids, an important and

interesting group of "id" manifestations includes toxic erythemas, sometimes scarlatiniform, exfoliative and universal in distribution; erythema multiforme-like eruptions, presumably due to the distribution of the fungi *via* the blood stream and their fulminating destruction in the hyperallergic skin; and including even extensive bullous and hemorrhagic eruptions. The clinical pictures long classified as pompholyx of the hands and dyshidrosis, in which, according to the views of the German and Swiss school, the causative fungus is absent in the overwhelming proportion of cases, are dermatophytids. An interesting controversy over the presence of the fungus in these lesions of the hands has developed over the American championship of the so-called "mosaic form," described by MacKee, Weidman and others, but interpreted by Continental observers largely as artefact (Becker and Ritchie, *Arch. Dermat. and Syph.*, 1930, **22**, 790; Jadassohn and Peck, *Arch. f. Dermat. u. Syph.*, 1929, **158**, 16; Cremer, *Ibid.*, 1933, **169**, 244).

It is important to realize that the secondary mycotic eruptions ("ids") may not only give rise to confusing pictures of eczema, erythema multiforme, toxic erythema and exfoliative dermatitis, but that they may be accompanied by constitutional symptoms, most frequently observed in connection with the granulomatous mycosis called *kerion Celsi*, a macaroon-like fungating tumor of the scalp, and including headaches, vomiting, anorexia, fever, marked regional adenopathy and leukocytosis.

Muende (*Post-Grad. Med.*, 1933, **9**, 197) summarizes the current conception of the sensitization mechanism involved in the production of the "phytid" by stating that fungous elements are thought to enter the blood stream and sensitize the skin and that later, at the height of development of the primary focus, showers of spores enter the blood stream, are destroyed in the skin to which they are distributed, giving rise to "ids" with various degrees of intensity of local reaction. The toxin of mycotic organisms, spoken of generically as trichophytin, also probably plays a part in this picture.

The range of clinical appearance of dermatophytids may be inferred from Muende's list—lichenoid follicular trichophytid in grouped arrangement; mycotic lichen spinulosus, corymbiform eruptions, annular eruptions, eczematoid and psoriasiform lichenoid eruptions, the dyshidrotic and pompholyx forms on the hand, scarlatiniform eruptions, desquamative postscarlatiniform pictures on the palms and soles, urticarial and erythema multiforme-like eruptions and erythema nodosum.

The Dermatophytoses.—While the most characteristic localization for these lesions containing the fungi is, of course, the hands and feet, particularly the interdigital spaces of the feet, primary foci may appear also at the anus, in the gluteal cleft, in the axillæ and the inguinal folds. Schmidt (*Arch. f. Dermat. u. Syph.*, 1933, **169**, 259) well illustrates the range in clinical appearance embraced in the modern classification of dermatophytoses of the hands and feet. He described 10 eruptions of the hands, due to epidermophytes, including interdigital erosions; the pseudodyshidrotic *epidermophyte* which produces vesicles along the contact surfaces of the fingers and on the backs of the fingers

and hands; a dry scaly type with impetiginous borders; localized eczematoid and fissured epidermophytosis of the palms and fingers; a dry squamous and fissured modification of the same type; grouped hyperkeratotic eczematous lesions of the fingers; eczematoid and fissured eruptions of the finger webs and knuckles; circumscribed, plaque-like, circinate and annular lesions of the backs of the hands and epidermophytosis with superposed dermatitis.

Moniliases and Oïdiomycoses.—This large group of yeast-like fungi has grown greatly in importance under recent investigative work. While yeasts can be grown from all parts of the skin and most of them are not pathogenic, BENHAM and HOPKINS (*Arch. Dermat. and Syph.*, 1933, **27**, 532) seem to have been able to single out Monilia albicans as the probable pathogen in the yeast-like dermatoses. This fungus was not obtained from the skin of 100 normal young adults, while other yeast-like organisms were obtained in 72%. On the other hand, the Monilia albicans is a well-recognized pathogen associated with a number of cutaneous pictures, including, in accordance with HOPKINS (*Arch. Dermat. and Syph.*, 1932, **25**, 599) detailed summary, erosio interdigitalis; paronychia of sporadic and epidemic types (the latter in fruit canners, Kingery and Chienes); perlèche (Finnerud, and Robinson and Moss); intertrigo in the distribution of tinea cruris and also under the breast, at the umbilicus and in the intergluteal and perianal folds. Additional monilia lesions of the skin include vulvitis (Guilini, Kehrer, Ferichs, Bloch and others), both of non-diabetic and diabetic types; a rare form of intertrigo of the toes (Weidman, Robinson and Moss); oral and cutaneous thrush in infants and children; moniliasis of the diaper region; moniliasis after continuous baths and wet dressings; moniliases of the tongue; moniliases of the vagina; balanoposthitis; non-intertriginous dermatitic moniliases of the forearms, nipples and tips of the fingers. Four of the most important and interesting groups of yeast infections of the skin as currently conceived include the well-known seborrheic eczema and seborrheic dermatitis, the so-called cryptococcosis epidermica and the moniliatids or levurids. Under seborrheic eczema should be mentiond the debated conceptions of Benedek, in which the cutaneous eruption is regarded merely as an outcropping of a general systemic infection with schizosaccharomyces hominis; the autoinoculable "seborrheic eczema" due to cryptococci (Cleveland White); and the form of seborrheic dermatitis associated with the presence of the Microsporon of Mallassez (MacLeod and Dowling), involving particularly scalp, neck and face. Cryptococcosis epidermica is a patchy, vesicosquamous eruption, widely scattered over the trunk and extremities and frequently with a predilection for seborrheic areas. It has been particularly discussed in the American literature by C. J. White and Schwartz. The group of moniliatids investigated principally by RAVAUT and RABEAU (*Presse méd.*, 1932, **40**, 1925) includes a group of mycotic intertriginous eruptions involving the inframammary and retroauricular folds and the umbilical region. The mycotic phase of this condition is the intertriginous eruption and associated with it may be found so-called eczematiform parakeratoses which are dry squamous dermatitic eruptions associated with secondary sensitization to the yeast fungi in the primary foci. Some interest

attaches to the frequency with which monilia appears in the gastro-intestinal tracts of patients with moniliform eruptions and also psoriasis, the suggestion being made that the intestinal focus contributes materially to the general sensitization responsible for the cutaneous manifestation.

Fungous-pyogenic Interrelations.—Much interest attaches to this group of cutaneous lesions, of which the chief clinical examples are the dermatophytosis-like eruptions of the hands from which no fungi can be obtained. These include especially dermatophytids, such as keratolysis exfoliativa, acrodermatitis perstans, amycotic eruptions of the hands and feet (Mitchell) and resistant pseudomycotic eruption of the feet (Andrews). In this group should be included also the so-called psoriasis pustulosa (Barber). This important group of troublesome and diagnostically confusible eruptions, distinguished either by their sterility to all culture methods or the impossibility of cultivating fungi from them, are in many cases clinically indistinguishable from typical culturally proved mycoses of the affected region. The studies of Ravaut and Rabeau have pointed to the presence of streptococcal complications in the so-called "levurid," in that bacterial organisms in cultures from the intertriginous "levurid" lesions, including several types of streptococci, may give rise to typical allergic and sensitization responses on intradermal injection.

Fungous-allergic Interrelations.—Several recent publications, including a paper by White and Taub (*J. Am. Med. Assn.*, 1932, **98**, 524) have directed attention to the predisposing effect of superficial fungus infections in inducing allergic dermatitis in susceptible persons. White cites a number of cases in which the preceding mycotic infection of the hands apparently prepared the way for allergic response to contact irritants, including cottonseed oil, oatmeal, buckwheat. This conception of interrelation between allergic manifestations and infections has, of course, been well recognized in the field of asthma and other allergic diseases.

Diagnosis of Mycotic Infections—Trichophytin Test.—Peck (*Discussion, Arch. Dermat. and Syph.*, 1932, **25**, 1118) has well summarized the process of diagnosing a cutaneous mycotic infection: "(1) In order to make a positive diagnosis instead of a presumptive one of fungus infection, the fungi, of course, must be demonstrated. The fungi should be found in the primary lesion and not in the trichophytids in the average case. The most difficult thing in a case of this kind is to make up one's mind where to look for the fungi, as it is almost impossible to determine where the epidermophytosis ends and the epidermophytids begin. Even in the primary lesions it is often possible to find the fungi only by culture. (See preceding summary.) (2) The trichophytin reaction should be strongly positive. While it is conceivable that there may be a positive anergy, it is not the rule. (3) A flaming up of the trichophytids even in the presence of a moderately positive trichophytin reaction is one of the best proofs for a diagnosis of epidermophytids. If one takes the casual dermatologic cases as they come into the clinic, in more than 50% a moderate degree

of hypersensitiveness to trichophytin is found; therefore, on a moderate reaction alone a diagnosis cannot be made. The control for the trichophytin must be used in the correct dilution to obviate pseudoreactions, and if the diluted trichophytin is allowed to stand too long it loses its potency." Peck has described a case of hemorrhagic trichophytids on the legs which developed after injections of trichophytin. Sulzberger pointed out that for adequate diagnostic testing oïdiomycin should be used as well as trichophytin, some patients reacting to only one and others to both. MUSKATBLIT and DIRECTOR (*Arch. Dermat. and Syph.*, 1933, **27**, 739), in an extended review of the trichophytin test, point out that there is as yet no standardized and universally recognized preparation of trichophytin either for diagnostic or therapeutic purposes. The usual dose of the available commercial preparations is 0.1 cc. of the undiluted extract on the flexor surface of the forearm. In 48 hours a negative test shows only a red dot at the site of injection or a pinkish macule no larger than the primary wheal ("depot" reaction). A weak positive is an erythematous patch, 2 to 4 cm. in diameter, and a strong positive shows an infiltration of one large or several small papules, at times vesicular in character and at times with a bright red halo. A positive reaction reaches its height in 48 hours and disappears in 1 week. Delayed reactions, disappearing in 3 to 5 days, increasing reactions, developing in from 3 to 7 days, and persistent reactions, lasting sometimes for several weeks, have been noted.

In 300 microscopically and culturally proved cases, these authors obtained 60.3% positive trichophytin tests, the tests being in agreement with the clinical diagnosis in 65.4% and in disagreement in 34.6%. The trichophytin test more frequently corroborated the clinical diagnosis than did the laboratory findings; 72.3% of the cases proved mycotic by the laboratory gave positive trichophytin reactions. Highly inflammatory lesions gave a high percentage of positive tests.

Prevention of Fungous Infection of the Feet.—The contributions of OSBORNE and HITCHCOCK (*J. Am. Med. Assn.*, 1931, **97**, 453), on the use of sodium hypochlorite, and of GOULD (*Ibid.*, 1931, **96**, 1300), on 10% sodium thiosulphate for the prevention of the transmission of mycotic infections of the feet in gymnasiums, shower baths and similar distributing centers for the dermatophytoses, deserves to be recalled. It is curious that the former authors noted sodium hypochlorite to have no treatment value in the concentration used, yet the preventive effect was so marked that no new cases of ringworm of the foot appeared in the Buffalo high schools after the trays, containing this solution, had been installed in the gymnasium showers. The sodium thiosulphate prophylaxis, proposed by Gould, is probably notably more expensive than that with sodium hypochlorite in large institutions.

Treatment of Fungous Infections.—Fungicidal methods recently proposed include the use of formaldehyde vapor for the sterilization and saturation of the leather of shoes and gloves, as proposed by HENDERSON (*Arch. Dermat. and Syph.*, 1932, **26**, 710). He points out that when shoes have been so treated during the night a distinct amelioration or disappearance of symptoms of mycotic infection on the feet begins the following day. The leather absorbs considerable amounts of the for-

maldehyd vapor. EMMONS (*Ibid.*, 1933, **15**, 21) found iodin and chlorin (surgical solution of chlorinated soda) to have the highest phenol coëfficient when tested against trichophyton and monilia suspensions. LEVINE (*J. Am. Med. Assn.*, 1933, **101**, 2109) used phenyl mercuric nitrate in tinea and yeast infections of the skin in 262 cases, of which 205 were cured. An ointment of equal parts of wool fat and an aqueous solution of the chemical in the strength of 1 to 1250 or 1 to 150 by weight, with the addition of 10% glycerin applied twice a day, was found most satisfactory. TAYLOR (*J. Am. Pharm. Assn.*, 1933, **22**, 410) found that the well-known effectiveness of potassium permanganate solution is probably due to the manganese rather than the permanganate element in the combination. Manganous sulphate, 1 to 1000, in water, gave much more striking results and 10% manganous oleate in anhydrous lanolin was also effective, but only when used on the foot. AYERS and ANDERSON (*J. Allergy*, 1933, **4**, 146) pointed out the frequent intolerance of Whitfield ointment as a cause of failure in the treatment of dermatophytosis. BARKSDALE (*Med. J. and Rec.*, 1932, **136**, 494) treated 80 negro children, on whom Roentgen ray could not be used, with 1% bismuth violet, 10% salicylic acid in 70% alcohol, using 1 to 2 coats of the dye applied daily without other dressing. The results were uniformly satisfactory, the patients being cleared of infection in 6 to 10 treatments.

The dangers of thallium epilation, when carried out under poorly controlled conditions in large institutions, is well illustrated by the appearance of several instances of poisonings, the worst example so far recorded being that of an orphan asylum in Granada, Spain, in which 14 children died (*Foreign Correspondence, J. Am. Med. Assn.*, 1933, **100**, 678).

The status of trichophytin as a therapeutic measure for desensitization is still in process of evaluation. VAN DYCK, KINGSBURY, THRONE and MYERS (*New York State J. Med.*, 1932, **32**, 1101) discuss in detail the technique of its administration and in a series of patients obtained cures in 30%, marked improvement in 33%, slight improvement in 32% and failure in 5%. SULZBERGER and WISE (*J. Am. Med. Assn.*, 1932, **99**, 1759) lean toward conservatism and while reporting desensitization in 15 out of 18 cases studied, only two-thirds of the number seemed benefited by the treatment on the basis of long remission or marked improvement or apparent cure. These authors produced no serious reactions in 100 patients treated with trichophytin but warn of the possibility of producing intractable, generalized exfoliative dermatitis, generalized eczema or even shock and fever. OSBORNE, PUTNAM and RICKLOFF (*New York State J. Med.*, 1933, **33**, 1270), after treating 100 cases of chronic relapsing ringworm infections of hands and feet with trichophytin, conclude that equally good results could have been obtained without trichophytin and that apparently good results later proved to be temporary. Furthermore these authors stress the importance of unfavorable reaction in the form of focal flare-ups, widespread dermatophytids, asthma and urticaria. The conclusion seems inevitably that the use of this agent is still in an experimental stage and its use requires great caution to avoid untoward reaction.

PHYSIOLOGY

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SESSION OF FEBRUARY 19, 1934

A Method for the Estimation of the Oxygen Content of One Cubic Millimeter of Blood.—JOHN S. DONAL, JR. (Laboratory of Pharmacology and the Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia). It has been observed (Donal, 1930) that the introduction of small amounts of a gas mixture containing oxygen into an evacuated space surrounding a heated tungsten filament results in the formation of positive ions at the filament surface. The ions so formed may be collected at a negatively charged electrode and the resulting current may be amplified and measured by means of a sensitive galvanometer. The galvanometer deflections have been found to be directly proportional to the amount of oxygen introduced into the filament chamber and independent, over a wide range, of the partial pressures of nitrogen and carbon dioxide in the gas mixture.

Samples of 1 cmm. of blood sealed in capillary glass tubes were extracted by breaking the tube in a high vacuum. The dried gases were then introduced into the filament chamber and the resulting galvanometer deflection compared with the deflection yielded by a sample of room air introduced in the same manner. The results of a series of such determinations were compared with the results of estimations made on large portions of the same samples of blood by the method of Van Slyke and Neill. After correction for a systematic error of +0.16 volumes per cent the average different between the results of 88 consecutive estimations and the values given by the Van Slyke method was 0.56 volumes per cent and the maximum difference encountered was 1.9 volumes per cent.

Oxygen Absorption Through the Skin.—SAMUEL GOLDSCHMIDT, BARTGIS MCGLONE and JOHN S. DONAL, JR. (Laboratories of Physiology and Eldridge R. Johnson Foundation, University of Pennsylvania). The following observations constitute convincing evidence that oxygen may penetrate the skin of the forearm, at least into the blood of the cutaneous vessels.

When the circulation is partially or completely occluded:

1. The normal color of the skin is maintained when the arm, in an atmosphere of oxygen, contains its usual amount of blood. The cyanosis which usually develops on the skin of an arm in air with arrested or impeded circulation is not in evidence except on some portions of the hand when the arm is in an atmosphere of oxygen.

2. The skin of the forearm, congested with blood, in oxygen is pink, in contrast to the bluish or dusky color of an arm in air, nitrogen or hydrogen under like conditions.

3. Under the above experimental conditions the skin color may be altered from normal to cyanotic or from pink to blue or *vice versa* by changing the gaseous atmosphere appropriately.

4. The oxygen content of the cutaneous blood of a forearm, in an atmosphere of oxygen, is invariably higher than it is when the arm is in nitrogen.

The Participation of the Neuroglia in Myelin Formation in the Prenatal Human Brain.—Bernard J. Alpers, and Webb Haymaker (Institute of Neurology, Pennsylvania Hospital). It is desirable to know the histologic elements concerned in myelin deposit in the brain. For this reason the brains of human fetuses ranging in age from 5 to 9 months were studied by silver methods for all forms of neuroglia and microglia and by methods for neutral fat, osmic acid fat and myelin. It was found that all the elements, astrocytes, oligoglia and microglia contain neutral fat from the fifth month on. Osmic acid fat is found only in the seventh and eighth stages. Myelin appears suddenly in the ninth month, but is not demonstrated before. Neutral fat is present in the bloodvessel endothelium in the fifth month.

The astrocytes are active in the myelinization process. Fat of all types is found in their cytoplasm at various stages. Myelin is found in the ninth month in the nerve cells and in the astrocytes. Furthermore, there seems to be a symbiotic relationship between the processes of the astrocytes and those of the nerve cells in the process of myelin deposit. These cells, therefore, play an important rôle in myelin deposit.

Potentials Produced in the Spinal Cord in Response to One and Two Stimuli.—Joseph F. Hughes and Herbert S. Gasser (Laboratory of Physiology, Cornell Medical College). Following stimulation of a dorsal root of a cat by a single induction shock there are set up in the spinal cord electrical potential changes, the complexity, form, and duration of which depend upon the experimental conditions obtaining at the time of the experiment. In deep ether narcosis the form of these potentials as recorded by the cathode ray oscillograph technique, when one lead is placed on the dorsal surface of the cord at the root level and the other several centimeters above, shows a period when the lead at the root level is negative followed by one in which it is positive to the more distal one. In light ether anesthesia additional negative crests make their appearance. The transition from the decerebrate to the spinal state is accompanied by an increase in the number and depth of these crests.

The magnitude of these potentials is greatest at the root level and falls off rapidly above and below it corresponding to the area of distribution of the collaterals of the primary neurone. Simultaneous stimulation of two adjacent homolateral roots gives evidence that the potentials are generated beyond a point where the two roots overlap. Antidromic stimulation of the motor horn cells through the sciatic nerve failed to affect the development of the cord potentials (as seen in leads from the dorsal surface of the cord) following stimulation of a dorsal root.

Recovery of the cord potentials after previous activity as studied through stimulation of the primary neurone did not begin until after

10σ had elapsed. Complete recovery did not occur until the electrical activity set up by the first stimulus had subsided, a time varying from 100σ to more than 880σ.

Comparison of the course of the cord potentials in response to a small conditioning and a large testing shock, with the size of the homolateral flexor reflex, shows that the cord potentials present a sufficiently typical background to enable one to predict the type of myographic response to the testing shock. The transition from reflex facilitation to "inhibition" has been shown to be accompanied by a transition in the form of the cord potentials. A negative wave with poorly developed crests followed by undeveloped positive wave goes with reflex facilitation while a negative wave with prominent crests and a well developed positive wave goes with reflex inhibition. The development and release from reflex inhibition are related to the mode of elimination and recovery of the late crests in the first negative complex of the cord potentials and can be explained largely on the basis of failure of excitation to reach the motor horn cells due to the interposition of refractory internuncial neurones.

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